



Inflammatory biomarkers and motoric cognitive risk syndrome: Multicohort survey

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ABSTRACT

Background: Inflammation may play a role in Motoric Cognitive Risk (MCR) syndrome, a pre-dementia syndrome comprised of slow gait and cognitive complaints. Our objective was to examine associations of inflammatory biomarkers with MCR.

Methods: We examined association of interleukin-6 (IL-6) and C-reactive protein (CRP) with prevalent MCR using logistic regression in 3,101 older adults (52% female) from five cohorts (National Center for Geriatrics & Gerontology Study of Geriatric Syndromes [NCGG-SGS], Central Control of Mobility in Aging [CCMA], Tasmanian Study of Cognition and Gait [TASCOG], LonGenity, and Einstein Aging Study [EAS]). Associations were reported as odds ratios adjusted for sex, age, education, depressive symptoms, body mass index, and vascular diseases (aOR) with 95% confidence intervals (CI). Meta-analysis and analyses stratified by vascular disease were also done.

Results: Although associations between higher (worse) CRP and IL-6 tertiles and MCR were only seen in three out of the five cohorts (EAS, TASCOG, and LonGenity), when a pooled meta-analysis was performed, a robust association was demonstrated. In meta-analysis, highest tertiles of IL-6 (aOR 1.57, 95%CI 1.01- 2.44) and CRP (aOR 1.65, 95%CI 1.09–2.48) was associated with MCR versus lowest tertiles in the pooled sample. Higher CRP was associated with MCR among those with vascular disease in TASCOG and LonGenity cohorts, and among those without vascular disease in EAS.

Conclusions: IL-6 and CRP levels are associated with MCR in older adults, and this association varies by presence of vascular disease.

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1. Introduction

Motoric Cognitive Risk (MCR) syndrome is a pre-dementia syndrome characterized by cognitive complaints and slow gait; first proposed in 2013 [1]. The predictive validity of MCR exceeds its cognitive or gait components taken individually, and even after accounting for the presence of mild cognitive impairment (MCI) [1,2]. Despite its clinical utility, the pathogenesis of MCR remains unknown. MCR is associated with risk of developing both Vascular Dementia and Alzheimer Disease [1, 3,4]. In line with these findings, risk factors for MCR include stroke, depressive symptoms, obesity, and low physical activity [1,5,6]. These risk factors share derangements in underlying inter-related biological pathways such as inflammation and oxidative stress, that co-occur in many diseases, including vascular disease [7]. Furthermore, vascular brain lesions such as white matter hyperintensities and subcortical infarcts are associated with both inflammation [8,9] and components of MCR (gait and cognition) [10,11]. These findings suggest that inflammation might also contribute to the pathogenesis of MCR [12–17].

MCR prevalence and associated risk factors may vary worldwide due to heterogeneity in population characteristics. Hence, we set out to perform a preliminary analysis of participants with biomarker data from five cohorts from three countries (USA, Japan, and Australia) in the MCR consortium. Our objective was to report the cross-sectional association between two inflammatory markers (interleukin-6 (IL-6) and C-reactive protein (CRP)) and MCR as a first step towards generating hypotheses, which could be tested in longitudinal studies. Given the established links between inflammation and vascular disease [18–21], we also examined the association between inflammatory markers and MCR in those with

and without vascular disease. We hypothesized that higher IL-6 and CRP levels would be associated with MCR, and that the association would be stronger among those with vascular disease than those without vascular disease. Establishing an association between inflammation and MCR will help elucidate the pathogenesis of MCR as a prelude to developing treatments in individuals with, or at risk for, MCR. This, in turn, may reduce the incidence, downstream, of dementia.

2. Materials and methods

2.1. Participants

This study includes data from five established cohorts within the MCR consortium. The goal of the MCR consortium funded by the National Institute on Aging is to determine the biological underpinnings of MCR. This study includes individual data from 1026 participants from the National Center for Geriatrics & Gerontology Study of Geriatric Syndromes (NCGG-SGS); 351 participants from the Central Control of Mobility in Aging Study (CCMA); 412 participants from the Tasmanian Study of Cognition and Gait (TASCOG); 433 participants from the LonGenity Study; and 879 participants from the Einstein Aging Study (EAS). Cohort details are summarized in Table 1. Eligibility criteria for each cohort are described elsewhere [1,22-25]. For this analysis, we included participants with at least one inflammatory marker data available. The determination of MCR status and collection of demographic and health data were during the same wave as the biomarkers. Participants with a diagnosis of dementia or who were unable to ambulate were excluded from this study. See Table 1 for dementia and gait criteria. This study

Table 1
Summary of MCR consortium Cohorts, Procedures, and Tests.

Variable	NCGG-SGS	CCMA	TASCOG	LonGenity	EAS
Location	Obu, Japan	NY, USA	Australia	USA	NY, USA
Study Baseline Year	2015–2016	2011	2004	2008	2002
Recruitment Age Eligibility	Aged ≥ 60 years old	Aged ≥ 65 years old	Aged 60 to 85 years	Aged ≥ 65 years old	Aged ≥ 70 years old
Cognitive Complaint	GDS memory item; questions from Cambridge Mental Disorders of the Elderly Examination (CAMDEX) questionnaire and the Subjective Memory Complaints scale[52–55]	GDS memory item; AD8	GDS memory item	GDS memory item*; Consortium to Establish a Registry for Alzheimer’s Disease (CERAD); [56] Health-self assessment [57]	GDS memory item*; Consortium to Establish a Registry for Alzheimer’s Disease (CERAD); Health-self assessment [57]
Dementia Diagnosis	Self-report	DSM-IV	Self-report	DSM-IV	DSM-IV
Gait Assessment	WalkWay MW-1000 instrumented walkway	GAITRite instrumented walkway	GAITRite instrumented walkway	GAITRite instrumented walkway	GAITRite instrumented walkway
Slow gait cuts (cm/s)					
Men 60–74 y	94.0	86.2	102.8	101.9	88.1
Men ≥ 75 y	81.4	76.4	86.0	85.3	72.3
Women 60–74 y	95.9	84.7	93.5	97.4	76.7
Women ≥ 75 y	81.7	66.1	71.9	76.7	66.5
Biomarker Assays					
IL-6 assay	Quanti Glow Human IL-6 Chemiluminescence ELISA kits, R&D Systems	Quanti Glow Human IL-6 Chemiluminescence ELISA kits, R&D Systems	Millipore Multiplex Cytokine Assays, Bioscientific, Pty	Quanti Glow Human IL-6 Chemiluminescence ELISA kits, R&D Systems	ultra-sensitive enzyme-linked immunosorbent assay, R&D Systems, Minneapolis, MN
CRP assay	IATRO CRP-EX, CRP Ultra Wide Range Reagent	Ultra Wide Range Reagent, Sekure Chemistry	Millipore Multiplex Cytokine Assays, Bioscientific, Pty	Ultra Wide Range Reagent, Sekure Chemistry	Ultra Wide Range Reagent Kit (Equal Diagnostics, Inc., Exton, PA, USA)
Prevalence of Parkinson’s Disease (%)	0.2	0.9	0.5	1.4	0.6

* GDS: Geriatrics depression scale item: “Do you feel that you have more problems with memory than most?” National Center for Geriatrics & Gerontology Study of Geriatric Syndromes [NCGG-SGS], Central Control of Mobility in Aging [CCMA], Tasmanian Study of Cognition and Gait [TASCOG], LonGenity, and Einstein Aging Study [EAS].

was approved by the institutional review board of the Albert Einstein College of Medicine. Each cohort site also obtained approval from their respective local ethics committees.

2.2. Dependent variable

The dependent variable was MCR. MCR is operationalized by four diagnostic criteria: (1) subjective cognitive complaints; (2) slow gait; (3) ability to ambulate; and (4) absence of dementia [1,2]. The presence of cognitive complaints was determined by interviewers in each cohort based on participant responses on standardized cognitive concern questionnaires; specific items are listed in Table 1. The GDS memory item was common to all cohorts, but additional cognitive complaint items that were available in individual cohorts were permitted to define subjective cognitive complaints to help identify a wider dementia at-risk pool. Gait speed measurement method and cut scores for slow gait are shown in Table 1. Cohort specific cut-offs for slow gait was selected because of the variability in gait speed across populations as well as by age and sex [26,27]. This approach is consistent with definition of slow gait used in our multi-country MCR prevalence study [2].

2.3. Independent variables

CRP and IL-6 were measured from stored frozen sera and plasma samples. IL-6 and CRP assay kits used in each cohort are listed in Table 1.

2.4. Other covariates

We selected demographic covariates (age, sex, years of education) to account for differences in cohorts and across cohorts. Additional variables included as covariates in analyses were body mass index (BMI), depressive symptoms measured by the Geriatric Depression Scale Short Form (GDS-S) and vascular disease. Vascular disease included a physician diagnosis of any one of diabetes, hypertension, stroke, and heart disease (myocardial infarction, angina or chronic heart failure). We include diabetes because it is associated with vascular manifestations such as retinopathy and atherosclerosis. We selected these clinical covariates based on previous studies showing that these clinical pathways might mediate the association between inflammation and MCR [8, 28-34]. Ethnicity was included as a covariate for the CCMA and EAS cohort analyses. Ethnicity in other cohorts was not included in cohort specific analyses due to homogeneity within each cohort of white Australian adults (TASCOG), Japanese adults (NCGG-SGS), and Ashkenazi Jewish adults (LonGenity).

2.5. Data analysis

Comparisons of demographic and health characteristics between participants with and without MCR were conducted in each cohort using chi-square tests or Fisher exact tests for categorical variables, and two-sample T-tests for continuous variables. Comparisons of median levels of biomarkers (non-normal distribution) between participants with and without MCR were conducted in each cohort using Mann Whitney tests. A series of logistic regression models were performed to test whether each biomarker was associated with MCR while adjusting for potential confounders (see above) in each cohort. Biomarkers were examined as continuous variables and as tertiles derived within each sample, where the reference group was always the lowest (least inflammation) group. All logistic regression models were adjusted for demographic (age, sex, education), and clinical data (BMI, depressive symptoms, and presence of any vascular disease), and reported as odds ratios (aOR) with 95% confidence intervals (95% CI). We also conducted logistic regression models stratified by the presence or absence of vascular disease.

Random-effects meta-analysis used adjusted beta and standard error from each individual cohort level model to pool adjusted odds of MCR across all five cohorts for IL-6 as continuous variable and categorical

variable (tertiles) and for CRP as continuous variable and categorical variable (tertiles). Thus, the meta-analysis was adjusted for the same major demographic variables as the analyses for each individual cohort. Heterogeneity between studies was tested using the χ^2 test and quantified by the I^2 statistic.

3. Results

3.1. Participant characteristics

Demographic characteristics of each cohort are presented in Table 2. Prevalence of MCR varied by cohort; 5.13% in CCMA, 7.02% in NCGG-SGS, 7.19% in TASCOG, 12.47% in LonGenity, and 11.04% in EAS. Across the cohorts, mean age ranged from 70.31 in NCGG-SGS to 79.54 in EAS. Participants with MCR were more likely to be older in the CCMA (mean age 81.43 vs 77.13, $p < 0.01$) and EAS (mean age 81.57 vs 79.29, $p < 0.01$) cohorts. Age did not differ by MCR status in the other cohorts. Participants in the TASCOG cohort had the lowest mean years of education (10.87 ± 3.66) and participants in the LonGenity cohort had the highest mean years of education (17.47 ± 2.81). Women comprised as few as 42.96% (TASCOG) and as much as 61.32% (EAS) of participants among the cohorts. Education and female sex did not differ between those with and without MCR within any cohort. Within CCMA, 77.49% of participants identified as non-Hispanic white, 17.66% identified as Non-Hispanic Black, and 4.84% identified as Other; there was no difference in MCR status by ethnicity in CCMA (not shown). Within EAS, 65.30% of participants were non-Hispanic White, 28.33% were non-Hispanic Black, and 6.37% were of another ethnicity. MCR was more prevalent among non-Hispanic Blacks (16.47%) than among non-Hispanic Whites (9.06%) or participants of other ethnicities (7.14%) in the EAS; $p < 0.01$.

3.2. Vascular disease

Vascular disease within each cohort is shown in Table 2. In TASCOG and LonGenity, those with MCR were more likely than those without MCR to report diagnoses of diabetes and hypertension. In NCGG-SGS, TASCOG and EAS, those with MCR were more likely than those without MCR to report history of stroke. In TASCOG and in EAS, participants with MCR compared to those without MCR were more likely to have experienced any heart disease. Those with MCR were more likely than those without MCR to report having at least one vascular disease in TASCOG, LonGenity, and EAS.

3.3. Other health variables

BMI was higher among those with MCR than those without MCR in the NCGG-SGS, LonGenity, and EAS) cohorts. Depressive symptoms were higher among those with MCR than those without MCR in all cohorts.

3.4. IL-6

Median IL-6 concentration ranged from 0.31 pg/mL in CCMA to 2.98 pg/mL in EAS. Table 3 summarizes associations of IL-6 with MCR within each cohort. The highest IL6 tertile was only associated with MCR in EAS (Table 3). IL6 as a continuous variable was not associated with MCR in any cohort.

Results of meta-analysis of IL-6 and MCR are shown in Fig. 1. In the meta-analysis, IL-6 as a continuous variable was not associated with MCR. However, compared to participants in the lowest tertile of IL-6, participants in the highest tertile (worse) of IL-6 did have increased odds of MCR in the pooled sample (aOR 1.57, 95% CI 1.01–2.44, $p = 0.04$).

Table 2
Participant characteristics within each cohort in the MCR consortium.

Variables	NCGG-SGS				CCMA				TASCOG				LONGENITY				EAS			
	Overall N = 1026	MCR N = 72	Non- MCR N = 954	P- value	Overall N = 351	MCR N = 18	Non- MCR N = 333	P- value	Overall N = 412	MCR N = 29	Non- MCR N = 383	P- value	Overall N = 433	MCR N = 54	Non- MCR N = 379	P- value	Overall N = 879	MCR N = 97	Non- MCR N = 782	P- value
Age, y	Mean ± SD 70.31 ±6.38	Mean ± SD 70.43 ±7.46	Mean ± SD 70.30 ±6.30	0.88	Mean ± SD 77.34 ± 6.50	Mean ± SD 81.43 ±7.28	Mean ± SD 77.13 ±6.40	<0.01	Mean ± SD 72.74 ±7.12	Mean ± SD 75.06 ±9.00	Mean ± SD 72.56 ±6.95	0.15	Mean ± SD 76.00 ±6.74	Mean ± SD 76.20 ±7.39	Mean ± SD 75.97 ±6.66	0.82	Mean ± SD 79.54 ± 5.37	Mean ± SD 81.57 ± 6.04	Mean ± SD 79.29 ± 5.23	<0.01
Education, y	11.68 ± 2.46	11.72 ±2.74	11.68 ±2.44	0.89	14.82 ± 2.93	14.44 ±2.71	14.84 ±2.94	0.58	10.87 ±3.66	10.04 ±2.79	10.93 ±3.71	0.21	17.47 ± 2.81	17.04 ±2.83	17.53 ±2.81	0.22	14.26 ± 3.41	13.85 ± 3.42	14.31 ± 3.41	0.20
BMI	23.62 ±3.13	25.01 ±3.49	23.52 ±3.08	<0.01	28.96 ± 7.54	31.82 ±9.16	28.80 ±7.42	0.10	27.83 ± 4.67	29.77 ± 7.06	27.69 ± 4.45	0.13	28.08 ±4.79	30.70 ±6.20	27.70 ±4.43	<0.01	27.58 ± 5.08	28.71 ± 4.96	27.44 ± 5.08	0.02
GDS-S	2.72 ±2.48	4.38 ±2.76	2.59 ±2.42	<0.01	2.25 ±1.98	3.72 ±2.24	2.17 ±1.93	<0.01	1.20 ± 1.69	2.75 ± 2.50	1.09 ± 1.56	<0.01	1.61 ±1.74	2.72 ±2.14	1.46 ±1.62	<0.01	2.14 ± 2.12	3.19 ± 2.80	2.01 ± 1.99	<0.01
Female	N (%) 503 (49.03)	N (%) 37 (51.39)	N (%) 466 (48.85)	P- value 0.68	N (%) 184 (52.42)	N (%) 10 (55.56)	N (%) 174 (52.25)	P- value 0.78	N (%) 177 (42.96)	N (%) 15 (51.72)	N (%) 162 (42.30)	P- value 0.32	N (%) 208 (48.03)	N (%) 24 (44.44)	N (%) 184 (48.55)	P- value 0.57	N (%) 539 (61.32)	N (%) 61 (62.89)	N (%) 478 (61.13)	P- value 0.74
Vascular Disease																				
DM	147 (14.33)	13 (18.06)	134 (14.05)	0.35	63 (17.95)	6 (33.33)	57 (17.12)	0.11	53 (12.86)	7 (24.14)	46 (12.01)	0.08	40 (9.28)	10 (18.51)	30 (7.96)	0.01	154 (17.64)	23 (23.71)	131 (16.88)	0.09
HTN	462 (45.07)	28 (39.44)	434 (45.49)	0.32	210 (60.2)	10 (55.56)	200 (60.42)	0.68	203 (49.27)	19 (65.52)	184 (48.04)	0.07	199 (50.13)	32 (65.31)	167 (47.99)	0.02	550 (63.00)	66 (68.04)	484 (62.37)	0.28
Stroke	47 (4.58)	11 (15.28)	36 (3.77)	<0.01	5 (1.43)	1 (5.56)	4 (1.20)	0.23	35 (8.50)	6 (20.69)	29 (7.75)	0.03	17 (3.95)	4 (7.41)	13 (3.46)	0.25	72 (8.25)	14 (14.43)	58 (7.47)	0.02
Cardiac	137 (13.35)	8 (11.11)	129 (13.52)	0.56	18 (5.13)	1 (5.56)	17 (5.11)	1.00	58 (14.08)	9 (31.03)	49 (12.79)	0.01	35 (8.10)	2 (3.70)	33 (8.73)	0.29	120 (13.75)	22 (22.68)	98 (12.63)	<0.01
Any Vascular Disease	588 (57.37)	41 (57.75)	547 (57.34)	0.95	229 (65.80)	13 (72.22)	216 (65.45)	0.56	242 (58.74)	24 (82.76)	218 (56.92)	<0.01	221 (56.09)	35 (71.43)	186 (53.91)	0.02	634 (72.62)	80 (82.47)	554 (71.39)	0.02

National Center for Geriatrics & Gerontology Study of Geriatric Syndromes [NCGG-SGS], Central Control of Mobility in Aging [CCMA], Tasmanian Study of Cognition and Gait [TASCOG], LonGenity, and Einstein Aging Study [EAS].

Table 3
IL-6 concentration and odds of MCR within each cohort in the MCR consortium.

NCGG-SGS			CCMA			TASCOG			LONGENITY			EAS			
n	Adjusted Odds of MCR		n	Adjusted Odds of MCR		n	Adjusted Odds of MCR		n	Adjusted Odds of MCR		n	Adjusted Odds of MCR		
	OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI	
IL-6 Continuous															
Overall															
1023	1.00	0.99, 1.01	331	0.40	0.09, 1.76	400	0.96	0.85, 1.09	200	0.98	0.93, 1.04	339	1.10	0.99, 1.21	
Any Vascular Disease															
545	1.02	1.00, 1.04	218	0.47	0.10, 2.17	235	0.97	0.86, 1.10	115	0.89	0.74, 1.08	239	1.09	0.98, 1.21	
No Vascular Disease															
437	0.99	0.95, 1.04	113	0.22*	<0.01, 50.58	165	1.02	0.59, 1.77	85	1.03	0.93, 1.14	100	1.15	0.79, 1.65	
IL-6 Tertiles															
Overall															
0	343	ref	ref	104	ref	ref	132	ref	ref	68	ref	ref	112	ref	ref
1 vs 0	340	0.73	0.37, 1.42	114	0.85	0.22, 3.30	134	1.04	0.31, 3.47	65	1.83	0.60, 5.59	113	2.12	0.75, 5.98
2 vs 0	340	1.28	0.69, 2.35	113	0.73	0.18, 2.97	134	1.67	0.53, 5.23	67	1.67	0.51, 5.50	114	3.59	1.32, 9.75
Any Vascular Disease															
0	178	ref	ref	56	ref	ref	65	ref	ref	30	ref	ref	66	Ref	ref
1 vs 0	195	0.57	0.22, 1.46	78	0.65	0.13, 3.18	88	0.66	0.15, 2.79	42	2.24	0.54, 9.36	76	2.42	0.70, 8.41
2 vs 0	213	1.40	0.63, 3.10	84	0.55	0.11, 2.75	82	2.18	0.60, 7.89	43	1.62	0.33, 7.86	97	4.08	1.24, 13.37
No Vascular Disease															
0	165	ref	ref	48	ref	ref	67	ref	ref	38	ref	ref	47	Ref	ref
1 vs 0	145	1.00	0.38, 2.64	36	1.47	0.10, 22.26	46	Unable to compute.		23	0.97	0.13, 7.36	37	1.11	0.14, 8.47
2 vs 0	127	1.22	0.46, 3.24	29	1.01	0.06, 18.34	52	Unable to compute.		24	2.05	0.27, 15.66	17	1.74	0.19, 16.05

* The maximum likelihood estimate may not exist.

3.5. CRP

Median CRP concentration ranged from 0.30 mg/L in NCGG-SGS to 2.00 mg/L in TASCOG. Table 4 summarizes associations of CRP with MCR within each cohort. CRP (continuous) was associated with increased odds of MCR in EAS among patients without any vascular disease (aOR 1.11, 95% CI 1.03–1.19). Significant associations of CRP tertiles with MCR were present in TASCOG and LonGenity, and EAS (Table 4).

Results of meta-analysis of CRP and MCR are shown in Fig. 1. In meta-analysis, CRP as a continuous variable was not associated with MCR. However, compared to participants in the lowest tertile of CRP, participants in the highest tertile (worse) of CRP did have increased odds of MCR in the pooled sample (aOR 1.64, 95% CI 1.09–2.48, $p = 0.02$).

4. Discussion

We examined the association between two pro-inflammatory markers, IL-6 and CRP, and prevalent MCR in five community-based aging cohorts from three countries within the MCR Consortium. We found that higher concentrations of IL-6 were associated with increased odds of MCR only in the EAS cohort, both overall and among those with vascular disease. Higher concentrations of CRP were associated with increased odds of MCR in three out of the five cohorts, TASCOG, LonGenity, and EAS. Although associations between the higher (worse) CRP and IL-6 tertiles and MCR were only seen in three of the five cohorts, when a pooled meta-analysis was performed, a robust association was demonstrated. In meta-analysis of all five cohorts, we found that those with the highest concentrations of IL-6 and CRP had increased odds of MCR. Interestingly, in stratified analyses, higher concentrations of CRP were associated with increased odds of MCR among those with vascular disease in TASCOG and LonGenity, and among those without vascular disease in EAS.

To the best of our knowledge, there has been limited examination of inflammatory biomarkers in the context of MCR. One previous study based in 5642 older adults participating in the China Health and Retirement Longitudinal study reported that higher CRP levels were associated with increased odds of prevalent MCR [16]. The association with CRP was stronger in MCR cases with memory impairment [16]. On the other hand, several studies have associated CRP and IL-6 levels to presence of MCI and risk of conversion to dementia [35–37].

Derangements in pro-inflammatory cytokines (such as IL-6 and CRP) in older adults have been linked to presence and/or risk of vascular disease and vascular risk factors such as obesity as well as depressive symptoms [18–21,31,34]. All these health factors in turn have been reported to predict MCR [3,38–40]. Hence, these clinical factors may mediate the relationship between inflammation and MCR [8,28–34]. However, even after adjusting for BMI, depressive symptoms, and vascular disease, the association of the inflammatory biomarkers with MCR were attenuated but remained (unadjusted models not shown); indicating that other unmeasured clinical pathways may also mediate this relationship.

We noted that the association of inflammation with MCR varied in the presence of vascular disease. Elevated concentrations of IL-6 were associated with MCR among those with vascular disease only in the EAS. Elevated concentrations of CRP were associated with MCR among those with vascular disease in TASCOG and LonGenity. These results favor a vascular pathway that links inflammation to MCR. Inflammation has been linked to risk of ischemic strokes [41] and white matter disease on neuroimaging [42, 43], which in turn has been linked to MCR [44]. The relationship of vascular risk factors and inflammation is bidirectional with higher vascular risk predicting progression of inflammation as well as white matter hyperintensities on neuroimaging [45]. However, Eastern and Western populations have different anatomical distributions of small vessel disease [46]; suggesting population specific factors that may determine pathogenesis of MCR regionally. Alternatively, in EAS, elevated CRP was associated with increased odds of MCR only among those without vascular disease, though the confidence intervals were broad due to the relatively small non disease vascular sample. However, another possibility given that mean age in EAS was the highest among the five cohorts is that a different process maybe at play at advanced ages [4,17,47–49]. The disassociation of IL-6 and CRP associations with MCR by presence of vascular disease also highlights that these two biomarkers may represent different inflammatory processes [50] or that underlying processes are incompletely captured in our study, which measured only two markers when many other inter-related inflammatory pathways and markers may be at play [51].

Limitations. Medical history was based on self-report. The number of co-morbidities included in our definition of vascular disease were limited based on availability across cohorts in the MCR consortium, and should not be viewed as exhaustive. We controlled for several potential clinical pathways that might mediate the association between

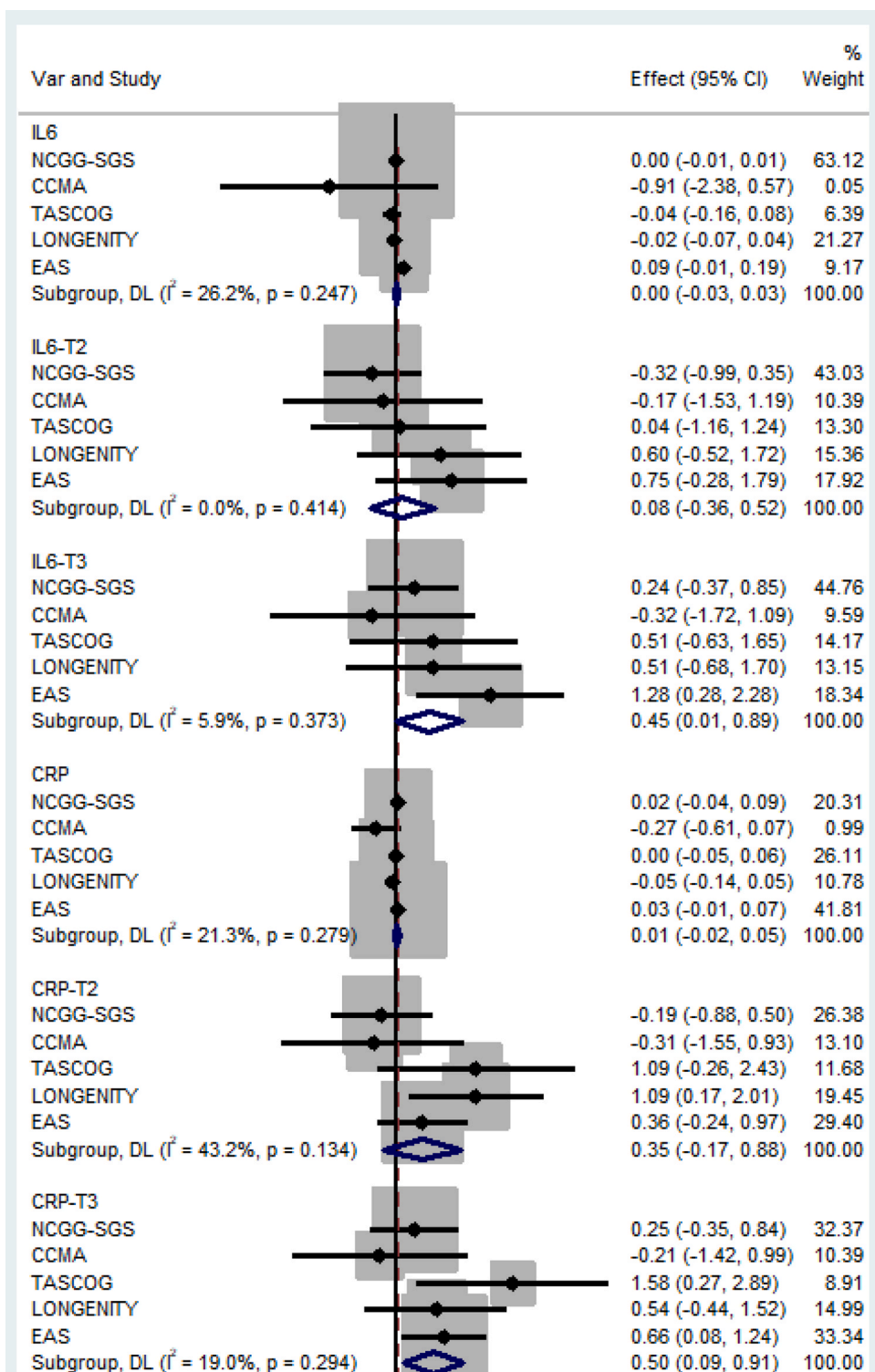


Fig. 1. Meta-analysis of associations of IL-6 (continuous and tertiles) and CRP (continuous and tertiles) with prevalent MCR in each cohort and pooled sample. Prevalence estimates (ES) for each study are graphically represented by dots and 95% confidence intervals by horizontal bars. gray boxes surrounding the dot graphically represent study weighting in the analysis, which is also shown in the last column. The diamond is the pooled prevalence estimate. Pooled effect estimate was similar for random- and fixed-effects model. The vertical dotted line represents the prevalence estimates of the pooled result.

inflammation and MCR, but other unmeasured confounders may be present. For example, data on physical activity, smoking or alcohol use was not available in all our cohorts, and should be examined in other populations. IL-6 and CRP have been extensively studied in the context of inflammation, vascular disease and cognitive decline, and were included in our analysis due to their availability in the MCR consortium. However, other inflammatory biomarkers and pathways may also play a role in the pathogenesis of MCR. As this is a cross-sectional study, we cannot establish causality or temporality.

Strengths include the availability of different populations in three countries in which the MCR definition was uniformly defined. The heterogeneity in populations is a strength that enabled us to build on previous single cohort and country studies that do not account for population differences in risk factors. The inflammatory marker ranges were specific to our cohorts, but the cut-scores and ranges provided should allow comparison with other cohorts.

Table 4
CRP concentration and odds of MCR within each cohort in the MCR consortium.

NCGG-SGS				CCMA			TASCOG			LONGENITY			EAS						
n	Adjusted Odds of MCR			n	Adjusted Odds of MCR		n	Adjusted Odds of MCR		n	Adjusted Odds of MCR		n	Adjusted Odds of MCR					
	OR	95% CI			OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI				
CRP Continuous																			
Overall																			
1023	1.02	0.96, 1.10		330	0.76	0.54, 1.08		402	1.00	0.95, 1.06		376	0.96	0.87, 1.05		827	1.03	0.99, 1.07	
Any Vascular Disease																			
586	1.02	0.94, 1.10		219	0.72	0.45, 1.13		236	1.01	0.95, 1.07		207	0.95	0.85, 1.07		601	1.01	0.96, 1.06	
No Vascular Disease																			
437	1.07	0.90, 1.26		111	0.87	0.53, 1.44		166	0.85	0.54, 1.33		169	0.97	0.82, 1.15		226	1.11	1.03, 1.19	
CRP Tertiles																			
Overall																			
0	410	ref	ref	106	ref	ref	137	ref	ref	125	ref	ref	278	ref	ref				
1 vs 0	267	0.83	0.41, 1.65	112	0.73	0.21, 2.54	142	2.96	0.77, 11.34	127	2.98	1.18, 7.49	276	1.44	0.78, 2.64				
2 vs 0	346	1.28	0.71, 2.32	112	0.81	0.24, 2.70	123	4.85	1.31, 18.00	124	1.72	0.65, 4.57	273	1.93	1.08, 3.47				
Any Vascular Disease																			
0	207	ref	ref	63	ref	ref	76	ref	ref	63	ref	ref	1185	ref	ref				
1 vs 0	164	1.23	0.51, 3.01	79	0.63	0.14, 2.93	86	1.97	0.45, 8.64	67	3.13	1.01, 9.77	207	1.18	0.61, 2.29				
2 vs 0	215	1.57	0.69, 3.570	77	0.87	0.22, 3.40	74	4.74	1.14, 19.71	77	1.24	0.38, 4.00	209	1.44	0.76, 2.74				
No Vascular Disease																			
0	203	ref	ref	43	ref	ref	61	ref	ref	62	ref	ref	93	ref	ref				
1 vs 0	103	0.36	0.10, 1.24	33	0.38	0.02, 6.63	56	Unable to compute.		60	3.25	0.57, 18.57	69	3.16	0.56, 17.79				
2 vs 0	131	0.97	0.40, 2.36	35	0.38	0.01, 12.05	49	Unable to compute.		47	4.37	0.67, 28.50	64	7.05	1.40, 35.46				

5. Conclusion

Our preliminary analyses indicate that IL-6 and CRP are associated with increased odds of MCR among community-dwelling older adults, and the association varied by the presence of vascular disease. Our cross-sectional findings should provide the foundation for longitudinal studies to establish the temporal associations of inflammation with MCR as well as provide insights into causality. A better understanding of the biological underpinnings of MCR will also help refine definitions of this syndrome by providing the possibility to reverse engineer definition of MCR based on emerging biological knowledge.

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Declaration of Competing Interest

The authors report no disclosures relevant to the manuscript.

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