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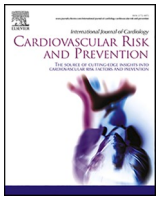

Myocardial infarction & C-reactive protein levels among Mexican adults with arthritis: Findings from the Mexican Health and Aging Study

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ABSTRACT

Background: Studies of adult populations in high-income countries have found an association between arthritis and myocardial infarction (MI) due to high levels of systemic inflammation. Our objectives were to examine the association between arthritis and MI among Mexican adults and to assess the mediating effect of C-reactive protein (CRP) on this association.

Methods: Data came from the 2012, 2015, and 2018 observation waves of the Mexican Health and Aging Study. Our sample included 11,707 participants aged 50 and older with no prior MI before 2012. We used self-reported information for arthritis, joint pain, medication use, and limitations to daily activities in 2012. Logistic regression was used to model the association between arthritis and self-reported MI in 2015 or 2018. We used a sub-sample of 1602 participants to assess the mediating effect of CRP.

Results: In the full sample, participants with arthritis that limited their daily activities had higher odds of MI than participants with no arthritis (OR = 1.40; 95 % CI = 1.04–1.88). In the sub-sample, arthritis that limited daily activities was associated with higher mean CRP (5.2 mg/dL; 95 % CI = 4.10–6.21) than arthritis with no limitations (3.5 mg/dL; 95 % CI = 2.93–4.01). However, CRP levels had a small mediating effect, and the relationship between arthritis with physical limitations and MI remained statistically significant.

Conclusion: Mexican adults with arthritis that limits their daily activities are at an increased risk for MI. Continued research is needed to identify factors that contribute to this increased risk.

1. Introduction

The prevalence of myocardial infarction (MI) in adults aged 60 and older is about 10 % globally [1]. Evidence from the United States and other high-income countries indicates that common types of arthritis, including rheumatoid arthritis, osteoarthritis, psoriatic arthritis, and gout, may be risk factors for MI [2,3]. The state of chronic systemic inflammation associated with different types of arthritis may play a major role in the development, instability, and rupture of atherosclerotic plaques leading to an MI [3,4].

Osteoarthritis is the most prevalent type of arthritis worldwide, with an estimated prevalence of 16 % globally in individuals aged 15 and older and 43 % in adults aged 40 and older [5,6]. Osteoarthritis is also the leading cause of physical disability for older adults [7]. Arthritis symptoms, such as pain and physical limitations, can limit a person's ability to perform daily activities and compromise their quality of life [8]. Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat arthritis pain; therefore, medication use may also be associated with moderate to severe symptomatic arthritis [9,10]. Symptomatic arthritis is associated with low-grade inflammation and increased inflammatory markers, such as C reactive protein (CRP), contributing to worsening symptoms [11–13]. This suggests that arthritis associated with pain, NSAID use, physical limitations, or a combination thereof, may be associated with higher levels of inflammation and therefore a higher risk for MI.

Few studies have investigated the association between arthritis and

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MI, especially in low-middle-income countries, such as Mexico. Many middle-aged and older adults in Mexico have worked in physically demanding jobs that can be detrimental to physical health and may increase the risk for arthritis later in life [14,15]. The prevalence of osteoarthritis and self-reported arthritis in Mexicans over the age of 40 ranges between 20 % and 25 % [16,17]. Cardiovascular disease (CVD) among Hispanics aged 40 and older has a prevalence ranging from 10 % for those without CVD risk factors to 70 % for those who have a history of diabetes mellitus, smoking, and dyslipidemia [18]. CVD is a major cause of death in Mexico, with ischemic heart disease accounting for about two-thirds of CVD deaths [19]. Given the high burden of arthritis and CVD in Mexico, we examined the association between arthritis and the risk of MI among middle-aged and older adults in Mexico with no prior history of MI. We also examined the potential mediating effect of CRP on the association between arthritis with physical limitations and MI among Mexican adults.

2. Methods

2.1. Data source and sample selection

This study is a longitudinal analysis of the 2012, 2015, and 2018 observation waves of the Mexican Health and Aging Study (MHAS). MHAS is a national longitudinal cohort of Mexican adults aged 50 and older and their spouses regardless of age. MHAS began in 2001 with a sample of 15,186 participants. Follow-up observations were completed in 2003, 2012, 2015, 2018, and 2021. New cohorts of participants were added in 2012 and 2018 to maintain the national representativeness of MHAS. Oral consent was obtained for each participant at every wave. Written informed consent was obtained for participants (n = 2086) whose blood was drawn in 2012. This study was completed following the Helsinki Declaration.

Supplemental eFig. 1a presents the selection of the final sample. A total of 15,723 participants aged 50 and older were interviewed in 2012 (our baseline); 1243 participants who completed a proxy-assisted interview were excluded because information about physical activity was not collected in the proxy interview. We excluded 507 participants who had an MI before 2012. We also excluded participants who were not observed at either follow-up wave (n = 1275) or were missing information for any of our covariates of interest (n = 165). The final sample included 11,707 participants aged 50 and older in 2012 who reported never having an MI and participated in at least one of the two follow-up waves (2015 or 2018).

We analyzed a sub-sample of 2086 participants (Supplemental eFig. 1b) whose blood was drawn in 2012. Data collected in the blood samples included CRP and cholesterol levels. Some participants (n = 83) were excluded because CRP was not collected from their blood samples. We also excluded participants (n = 400) who either had an MI before 2012 or whose MI status was not reported. We decided to exclude any participants with a CRP value > 100 mg/dL (n = 1) to eliminate possible measurement errors or participants with severe inflammation more likely from an acute infectious process rather than a rheumatological condition [20]. The final sub-sample had 1602 participants with a mean CRP of 3.96 mg/dL ranging from 0.02 mg/dL to 66.88 mg/dL.

2.2. Measures: primary variables

Arthritis. MHAS participants were asked questions about health conditions, including arthritis and MI. Arthritis was self-reported by participants who were first asked, "Has doctor or medical personnel ever diagnosed you with arthritis or rheumatism?" (yes or no). Participants who responded "yes" were then asked the following questions: 1) "Do you feel pain, stiffness, or swelling in your joints?" (yes or no), 2) "Are you taking medication or are you receiving other treatment for your arthritis or rheumatism?" (yes or no), and 3) "Are your daily activities, such as household chores or your job, limited because of your arthritis?" (yes or no). We used these questions to further categorize arthritis into three distinct variables: arthritis with or without pain, arthritis with or without medication use, and arthritis with or without physical limitations. All arthritis variables were assessed at our baseline wave in 2012.

Myocardial infarction. Participant's MI status was also self-reported and assessed by the question, "Has a doctor or medical personnel ever told you that you have had a heart attack?" (yes or no). Any participants who answered "yes" in either the 2015 or 2018 follow-up waves were classified as having ever developed an MI.

C-reactive protein. CRP was measured via blood sample in mg/L using the MULTIGENT CRP Vario assay. CRP was collected from a sub-sample of participants (n = 1602) during the 2012 wave only.

2.3. Measures: covariates

Selected covariates included demographic characteristics and self-reported health behaviors and conditions known to be risk factors for an MI [21]. Demographic variables were age, sex, and years of education. Self-reported health behaviors were physical activity levels (<3 times per week or ≥ 3 times per week) and smoking (never smoker vs ever smoker). Self-reported health conditions were hypertension and diabetes mellitus. Lastly, body mass index (BMI) was calculated based on height and weight measurements of participants in 2012. We used a BMI ≥30 kg/m^2 to categorize participants as obese vs non-obese. For our sub-sample analysis, we also used blood cholesterol levels (≥240 mg/dL) to categorize participants as having hyperlipidemia (HLD).

2.4. Statistical analyses

Descriptive characteristics of our sample were reported according to arthritis status. We used a *t*-test or analysis of variance (ANOVA) for continuous variables (age, education, and CRP) and chi-square tests for categorical variables. The association between arthritis and developing an MI was assessed using logistic regression models to report the odds ratio (OR) and 95 % confidence interval (CI). We first modeled the association between arthritis in 2012 and ever having an MI in 2015 or 2018 while adjusting for other known risk factors for MI. We also conducted separate multivariate analyses to model the association of arthritis with and without pain, arthritis with and without medication use, and arthritis with and without physical limitations with MI, adjusting for covariates.

We followed the Baron & Kenny method to determine whether CRP levels mediate the relationship between arthritis with physical limitations and MI [22]. First, we used logistic regression to model the association between arthritis with physical limitations and MI, adjusting for demographic and health characteristics. Next, we compared the average CRP levels in 2012 for participants who experienced an MI to those who did not. Finally, we used a second logistic regression to model the association between arthritis with physical limitations and MI, adjusting for CRP levels. The change in the coefficient for arthritis with physical limitations when adjusting for CRP levels compared to the same coefficient without adjusting for CRP levels represents the mediating effect of CRP. All analyses were done using Stata/SE version 17.

3. Results

As shown in Table 1, the prevalence of self-reported physician-diagnosed arthritis in our sample was 13.8 %. Of the participants who reported having arthritis (n = 1613), 1431 (88.7 %) reported having pain and stiffness associated with their arthritis, 1015 (62.9 %) reported taking medications to treat their arthritis, and 815 (50.5 %) reported having physical limitations to their daily activities due to arthritis. The average age of our sample was 64.3 years, and 4901 (41.9 %) were male. The mean years of education received by participants was 5.7 years. Most participants were not physically active (59.8 %). A total of 2968 (25.4 %) participants were obese (BMI ≥30 kg/m^2). A total of 4324

Table 1
Descriptive characteristics of the sample by the presence of arthritis in Mexican adults (N = 11,707).

Variables	Total N (%)	No Arthritis N (%)	Arthritis N (%)	P value
Total	11,707 (100.0)	10,094 (86.2)	1613 (13.8)	
Pain with Arthritis	1431 (12.2)	N/A	1431 (88.7)	
Medication for Arthritis	1015 (8.7)	N/A	1015 (62.9)	
Physical Limitations with Arthritis	815 (7.0)	N/A	815 (50.5)	
Age (years), mean ± SD	64.3 ± 9.1	63.9 ± 9.1	66.7 ± 9.0	<0.001
Sex (Male)	4901 (41.9)	4463 (44.2)	438 (27.2)	<0.001
Education (years), mean ± SD	5.7 ± 4.7	5.8 ± 4.8	4.8 ± 4.2	<0.001
Physical Activity (<3 times/week)	6997 (59.8)	5918 (58.6)	1079 (66.9)	<0.001
Ever Smoking	4324 (36.9)	3811 (37.8)	513 (31.8)	<0.001
Obesity (BMI ≥30 kg/m^2)	2968 (25.4)	2495 (24.7)	473 (29.3)	<0.001
Hypertension	5020 (42.9)	4140 (41.0)	880 (54.6)	<0.001
Diabetes Mellitus	2584 (22.1)	2213 (21.9)	371 (23.0)	0.333
Myocardial Infarction	516 (4.4)	425 (4.2)	91 (5.6)	0.009

SD: standard deviation; BMI: body mass index; N/A: not applicable.

(36.9 %) participants did ever smoke, 5020 (42.9 %) reported hypertension, and 2584 (22.1 %) reported diabetes mellitus. A total of 516 (4.4 %) participants reported having an MI in either 2015 or 2018. There were significantly higher percentages of participants with arthritis who reported an MI compared to participants without arthritis (p = 0.009). Participants with arthritis were older, more likely to be female, less educated, less physically active, more obese, more likely to have hypertension, and less likely to have ever smoked compared to participants without arthritis.

Table 2 shows the ORs and 95 % CIs for the multivariate association between arthritis and MI. Unlike the univariate association (OR = 1.36; 95 % CI = 1.08–1.72; p = 0.010), participants with arthritis did not have statistically significant higher odds for MI (OR = 1.20; 95 % CI = 0.95–1.53; p = 0.129) compared to participants without arthritis, after adjusting for covariates. This multivariate model shows that participants who are older (OR = 1.03; 95 % CI = 1.02–1.04; p < 0.001), male (OR = 1.48; 95 % CI = 1.20–1.81; p < 0.001), with hypertension (OR = 2.24; 95 % CI = 1.85–2.72; p < 0.001), and with diabetes mellitus (OR = 1.54; 95 % CI = 1.27–1.88; p < 0.001) had statistically significant higher odds for an MI compared to participants who were younger, female, without hypertension, and without diabetes mellitus, respectively.

Table 2
Multivariate model of arthritis associated with myocardial infarction among Mexican adults (N = 11,707).

Predictor Variables	Myocardial Infarction OR (95 % CI)	P value
Arthritis	1.20 (0.95–1.53)	0.129
Age (years)	1.03 (1.02–1.04)	<0.001
Sex (Male)	1.48 (1.20–1.81)	<0.001
Education (years)	1.01 (0.99–1.03)	0.515
Physical Activity (<3 times/week)	1.07 (0.88–1.29)	0.499
Ever Smoking	1.05 (0.86–1.28)	0.628
Obesity (BMI ≥30 kg/m^2)	1.21 (0.99–1.48)	0.061
Hypertension	2.24 (1.85–2.72)	<0.001
Diabetes Mellitus	1.54 (1.27–1.88)	<0.001

OR: odds ratio; CI: confidence interval; BMI: body mass index.

In the multivariate models of arthritis characteristics and MI shown in Fig. 1, the participants who reported arthritis with physical limitations had statistically significantly higher odds of developing an MI (OR = 1.40; 95 % CI = 1.04–1.88; p = 0.028) compared to participants without arthritis. Reported arthritis with pain (OR = 1.18; 95 % CI = 0.92–1.52; p = 0.203) did not show statistically significant increased odds for MI. Similarly, participants with arthritis who are either taking medications (OR = 1.19; 95 % CI = 0.89–1.60; p = 0.235) or not taking medications (OR = 1.22; 95 % CI = 0.85–1.76; p = 0.285) did not show significantly higher odds for MI in the multivariate analyses.

Supplemental eTable 1 shows the descriptive characteristics of the sub-sample used to test the mediating effects of CRP on the relationship between arthritis with physical limitations and MI. The prevalence of self-reported arthritis with physical limitations and arthritis without physical limitations was 7.3 % and 6.6 %, respectively. The mean CRP of the overall sub-sample was 4.0 mg/dL (SD = 5.1). The average age of the sub-sample was 63.0 years, and 657 (41.0 %) participants were male. The mean years of education obtained was 5.7 years. Most participants (n = 867) were not physically active (54.1 %). A total of 440 (27.5 %) participants were obese (BMI ≥30 kg/m^2). A total of 616 (38.5 %) participants did ever smoke, 667 (41.6 %) reported hypertension, 350 (21.9 %) reported diabetes mellitus, and 259 (16.2 %) had HLD. The mean total cholesterol and high-density lipoprotein (HDL) cholesterol were 202.1 mg/dL (SD = 45.1) and 41.4 mg/dL (SD = 10.4), respectively. A total of 75 (4.7 %) participants reported having an MI in either 2015 or 2018. A significantly higher percentage of participants with arthritis and physical limitations reported an MI compared to participants with arthritis and no physical limitations or participants without arthritis (p = 0.010).

Fig. 2 shows a significantly higher (p = 0.022) mean CRP among participants with arthritis and physical limitations (5.2 mg/dL; 95 % CI = 4.10–6.21) compared to participants with arthritis and no physical limitations (3.5 mg/dL; 95 % CI = 2.93–4.01). Participants without arthritis had a significantly lower (p = 0.012) mean CRP (3.9 mg/dL; 95 % CI = 3.63–4.17) compared to participants with arthritis and physical limitations. There was a statistically significant difference in the mean CRP between participants with arthritis and physical limitations and participants with arthritis and no physical limitations (p = 0.006). However, there was no statistically significant association between CRP levels and MI (p = 0.249).

Supplemental eTable 2 shows the ORs and 95 % CIs for the multivariate association between arthritis with physical limitations and the odds of developing an MI over 6 years of follow-up. After adjusting for other risk factors, Model 1 shows that participants with arthritis and physical limitations had significantly higher odds for MI (OR = 2.22; 95 % CI = 1.13–4.36; p = 0.021) compared to participants without arthritis. Model 1 also shows that participants with hypertension (OR =

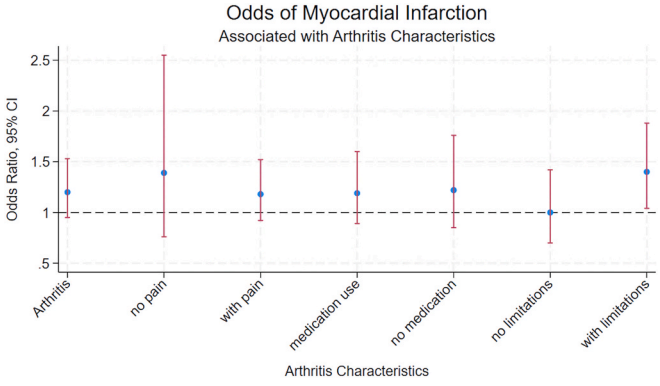

Fig. 1. Multivariate models of arthritis associated with myocardial infarction among Mexican adults (N = 11,707).

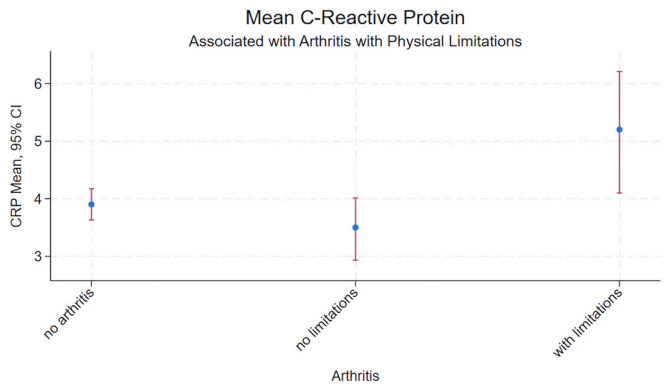

Fig. 2. Mean CRP associated with arthritis with physical limitations among Mexican adults (N = 1602).

3.18; 95 % CI = 1.87–5.42; $p < 0.001$) and diabetes mellitus (OR = 1.68; 95 % CI = 1.00–2.80; p = 0.048) had statistically significantly higher odds of MI compared to participants without hypertension and diabetes mellitus, respectively. Model 2 shows the multivariate association between arthritis with physical limitations and MI after adjusting for CRP. Participants with arthritis and physical limitations continued to have significantly higher odds for MI (OR = 2.19; 95 % CI = 1.11–4.30; p = 0.023) compared to participants without arthritis. In Model 2, hypertension remained statistically significant (OR = 3.20; 95 % CI = 1.88–5.48; $p < 0.001$) but diabetes mellitus did not (OR = 1.64; 95 % CI = 0.98–2.75; p = 0.060).

4. Discussion

Evidence from cohort studies of aging in high-income countries indicates that common types of arthritis, such as rheumatoid arthritis and osteoarthritis, are associated with an increased risk for MI [23,24]. Our study adds to existing epidemiological research by using data from a nationally representative cohort of middle-aged and older adults in Mexico and by focusing on possible clinical indicators of this association, including joint pain, medication use, and physical limitations. We found that participants with arthritis that physically limited their daily activities, and no prior history of MI, had a significantly higher risk for MI over 6 years compared to participants with no arthritis, even after adjusting for sociodemographic and health characteristics known to be CVD risk factors [21]. Furthermore, participants with arthritis but no limitations in daily activities did not have a significantly higher risk for MI compared to participants with no arthritis. These findings suggest that arthritis that limits a person's ability to complete daily activities may be a clinical indicator of increased MI risk among the Mexican population.

In our unadjusted analysis, self-reported arthritis was associated with a 36 % higher risk for MI compared to no arthritis. However, in the multivariate analysis, arthritis was no longer significantly associated with a higher risk of MI after adjusting for demographic characteristics, comorbid health conditions, and health behaviors. Arthritis is a frequent comorbid condition with other chronic diseases, such as hypertension and type 2 diabetes mellitus, especially among Mexican adults [25,26]. Obesity is also associated with an increased risk for arthritis [27]. Obesity and chronic diseases, such as hypertension and type 2 diabetes mellitus, are well-established risk factors associated with an increased risk for MI [21]. This evidence suggests that obesity and chronic conditions may be mediating the association between self-reported arthritis and MI risk among Mexican adults.

We did not find evidence that the risk of MI was significantly different for participants with arthritis who also reported joint pain. Unlike other studies, approximately 88 % of our participants with arthritis also reported experiencing joint pain. Most older adults report experiencing joint pain [28], but usually 5 %–20 % of older adults with arthritis report symptomatic joint pain [29]. We found no difference in the association between arthritis and the risk of MI based on taking medications for arthritis. Older adults often take medications for joint pain. In fact, NSAIDs are nearly universally recommended as first-line treatment for joint pain, especially in osteoarthritis [30]. Most (63 %) of our participants with arthritis reported taking medication for their arthritis. The majority of these participants could be taking NSAIDs. If this is the case, NSAID usage is higher than in US population-based studies in which 24 %–36 % of older adults with arthritis reported taking an NSAID [31]. NSAIDs are well known for their cardiovascular effects, including increased risk of MI and heart failure [32]. But due to their anti-inflammatory properties, NSAID use has also been shown to be beneficial in reducing the risk of recurrent MI in patients with stable coronary heart disease [33]. In patients with gouty arthritis, allopurinol and febuxostat are commonly used drugs that have increased incidences of cardiovascular effects; however, observational studies have shown cardiovascular benefits in the treatment of gout compared to non-treated participants, especially among patients taking colchicine [34,35]. In patients with rheumatoid and psoriatic arthritis, the use of disease-modifying antirheumatic drugs (DMARDs), such as tumor necrosis factor (TNF) inhibitors and methotrexate, may reduce the risk of cardiovascular disease, including MI [36]. Lastly, steroids may increase MI risk by increasing weight gain, hypertension, hyperlipidemia, and insulin resistance, but may also decrease MI risk, as they decrease overall inflammation [37].

The mean CRP among participants with arthritis and physical limitations was significantly higher than the mean CRP among participants with arthritis and no physical limitations. This finding suggests that participants with arthritis who have daily physical limitations have an associated increase in systemic inflammation, which, as other studies have concluded, places them at a higher risk for MI [38]. CRP at baseline was not associated with risk of MI over 6 years of follow-up. The inclusion of CRP made a difference of 1.4 % between the ORs reported for MI among participants with arthritis and physical limitations. With such a minimal impact on the association between arthritis with physical limitations and MI, we do not have enough evidence to support that inflammatory markers, such as CRP, are effect modifiers for this association. Further studies should be done to examine the mediation effect of CRP levels on the association between arthritis with physical limitations and the risk of MI over time.

Our analysis produced new evidence on the association between arthritis and MI risk among adults in Mexico with no prior history of MI. Our prospective study design allowed us to confidently conclude a temporal relationship between self-reported arthritis (diagnosed before the completion of the 2012 wave), CRP (collected at the 2012 wave), and MI (collected in 2015 and 2018). Our results, however, need to be interpreted with some caution given important limitations. First, MHAS participants are not asked about the time of diagnosis, duration, or specific type of arthritis. The risk of MI varies across different types of arthritis, with rheumatoid arthritis having the highest risk [3]. A second limitation is that MHAS does not collect definitive diagnostic indicators, such as anti-cyclic citrullinated peptide or troponin, for the diagnosis of arthritis and MI. Instead, MHAS uses only self-reported information, which is subject to misreporting and possible bias [39]. Our use of self-reported information for MI also means that our study only includes participants who survived their MI and participated in the follow-up observation waves. A third limitation is that MHAS participants are not asked to give information about the type of medications or how many medications they were taking for arthritis or any co-morbid condition at the time of the interview. The anti-inflammatory properties of medications such as NSAIDs, beta-blockers, and DMARDs may be potential confounders not adjusted for in this study [40]. A fourth limitation is that MHAS does not collect information on healthcare utilization related to MI, complications from MI, and potential important behaviors, such as the type of physical activity performed by MHAS

participants. Such information would have allowed us to conduct more nuanced analyses of the association between arthritis and MI risk. Lastly, we only collected CRP levels in 2012, and we do not have information about participants' CRP levels at the time of their MI. The lack of recurrent CRP measurements limits our ability to assess the mediating effect of CRP on the association between arthritis with physical limitations and MI over time.

5. Conclusion

Our analysis of Mexican adults aged 50 and older revealed that arthritis with physical limitations to daily activities is associated with an increased risk for MI over six years. Our results provide evidence that physical limitations may be a clinical marker for increased MI risk among older adults with arthritis. Our results also suggest that arthritis with physical limitations might be associated with a higher degree of systemic inflammation, which may be a plausible mechanism for the increased risk for MI. However, it is unclear how much of this risk is due to inflammation, physical inactivity, or other factors. Future research is needed to identify causal mechanisms that contribute to an increased risk for MI among middle-aged and older adults with arthritis, especially in low-middle income countries.

Statements and declarations

The authors have declared that no conflict of interest exists.

CRediT authorship contribution statement

Alan F. Villarreal Rizzo: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Elizabeth I. Davis:** Writing – review & editing, Writing – original draft. **Wissam I. Khalife:** Writing – review & editing, Conceptualization. **M. Kristen Peek:** Writing – review & editing, Validation. **Brian Downer:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Conceptualization.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcrp.2024.200309.

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