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Ethnic Disparities in Atherosclerotic Cardiovascular Disease Incidence and Prevalence Among Rheumatoid Arthritis Patients in the United States: a Systematic Review

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Objective. Rheumatoid arthritis (RA) is associated with increased atherosclerotic cardiovascular disease (ASCVD). General population cohorts have shown African American individuals to have greater and Hispanic Americans to have lower cardiovascular disease prevalence when compared with non-Hispanic white individuals; however, the reasons for these findings are not clear. This systematic review seeks to describe the incidence and prevalence of ASCVD stratified by race/ethnicity within the US RA population.

Methods. MEDLINE, Embase, and Cochrane databases were searched for studies that reported incidence or prevalence of ASCVD (including, but not limited to, fatal and nonfatal stroke, myocardial infarction, and cardiovascular death) in those with RA. Abstracts and full texts were screened separately for inclusion by two reviewers, with a third reviewer to resolve discrepancies.

Results. We screened 2625 abstracts and fully reviewed 138 manuscripts. Twenty-one were included that cited at a minimum the percentage of non-Hispanic whites in their population. No publication meeting entry criteria initially stratified ASCVD by race/ethnicity. The average prevalent ASCVD in RA is 46.9% (95% CI: 46.8–47) (range of prevalent ASCVD: 30%-47%). The average incident ASCVD is 8.2% (95% CI: 8.14–8.25) (range of incident ASCVD 1%–46%).

Conclusion. In this systematic review, we found a paucity of data on racially/ethnically diverse RA patients and ASCVD outcomes. Future studies should report the prevalence of ASCVD in various races/ethnicities with RA in the United States. These data would help inform clinicians on how best to manage cardiovascular disease risk in RA.

INTRODUCTION

Rheumatoid arthritis (RA) is known to carry a substantially increased risk of atherosclerotic cardiovascular disease (ASCVD). RA and ASCVD share the common pathophysiology of increased inflammation (1–5), which may contribute to the observed increased cardiovascular mortality in patients with RA (1,6). Overall mortality rates in patients with RA are 1.5 to 1.6 times higher than in patients without RA (2,7–11), and, therefore, mitigation of cardiovascular risk in RA could significantly improve morbidity and mortality. More recent data from the United Kingdom and United States have shown an improvement over the years in cardiovascular disease mortality in patients with RA, but overall mortality rates in RA may still be higher than that observed in the general population (12–14).

Racial and ethnic minorities in the general population have a higher prevalence of ASCVD compared with non-Hispanic white (NHW) individuals (15), which raises the question of whether minorities with RA are at an even higher risk of ASCVD. For instance, African American individuals (AAs) with any kind of connective

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SIGNIFICANCE & INNOVATION

- This study demonstrates the need for future rheumatoid arthritis studies in more ethnically diverse populations.
- Investigators should report incidence or prevalence data stratified by race/ethnicity.
- Additional data are needed in order to determine the presence and extent of ethnic disparities in atherosclerotic cardiovascular disease within the US rheumatoid arthritis population.

tissue disease (CTD) are at further elevated risk for ASCVD compared to both minorities without CTD and NHW with CTD (16). It is thought that this elevated ASCVD risk may also be present in AA with RA (17). In contrast, Hispanics with RA have higher inflammation-related indices and traditional cardiovascular risk factors yet similar rates of ASCVD as compared with NHW (18). This "Hispanic paradox" has also been observed in those without RA (19). The mechanisms of varying ASCVD prevalence in different races or ethnicities are unclear, and they warrant further study. This systemic literature review seeks to identify studies stratifying ASCVD by race/ethnicity in RA.

METHODS

Literature search strategy. Four electronic databases (Ovid MEDLINE, Ovid MEDLINE In-Process/EPub Ahead of Print, Ovid Embase, and the Cochrane Library) were searched from inception of study to April 26, 2020, using search terms described in the Supplementary Methods. In addition, American College of Rheumatology (ACR) and European League Against Rheumatism Conference Abstracts using Embase were searched from 2017 to April 26, 2020. The study was conducted in accordance with Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (20).

Eligibility criteria. Studies that met the following criteria were included: 1) evaluated patients with RA diagnosed using billing codes (International Classification of Disease [ICD]-9 and ICD-10 codes), physician's diagnosis, ACR guidelines, seropositivity and disease-modifying antirheumatic drug use, and self-diagnosis; 2) reported the incidence or prevalence of one or more manifestations of ASCVD (diagnosed using billing codes, manual adjudication by trained reviewer, guidelines). Studies were excluded if they 1) characterized a cohort that was not residing in the United States; 2) only examined nonatherosclerotic-mediated cardiovascular disease; 3) did not mention race or ethnicity; 4) had insufficient data to determine necessary denominator for prevalence; 5) were a case report, commentary, or review article; 6) contained nonhuman data; 7) evaluated children 17 years of age or younger; and 8) were not in the English language. For multiple publications that analyze similar or identical cohorts, such as large registries, we included the largest sample size, which was preferably, but not always from a more recent cohort.

ASCVD was defined as fatal and nonfatal stroke, angina, myocardial infarction (ST or non-ST elevation), atherosclerotic plaque, ischemic heart disease, coronary artery disease, coronary artery bypass graft, percutaneous coronary intervention, peripheral arterial disease, peripheral vascular disease, revascularization, carotid stenosis, cardiovascular mortality, and cardiovascular death. Diagnoses of chest pain, transient ischemic attack, heart failure, diastolic dysfunction, cardiomyopathy, valvular disease, and pericardial disease were excluded.

Study selection and data extraction and synthesis. After removing duplicates, two investigators (C.M.D. and L.D.) independently assessed studies for eligibility and extracted data as dictated by the research question. Abstracts were screened initially for relevance, followed by full text review to assess for inclusion. A third reviewer (E.B.S.) was available to resolve discrepancies between the two primary reviewers. Using a template, the primary reviewers (C.M.D. and L.D.) independently catalogued data, including the number of patients, study design, race/ethnicity, and types of ASCVD measured. Of note, no publication stratified ASCVD by race/ethnicity, thus three reviewers (C.M.D., E.B.S., and U.E.M.) emailed the corresponding authors for studies that mentioned ethnicity and ASCVD in their full texts for additional data sharing, and relevant data was included when provided. To assess study quality, we used the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-sectional Studies (21). This tool contains 14 criteria that assess study design, relevant statistical analysis, and appropriate evaluation of exposure and outcome (see Supplementary Table 1). The criteria are added up, with a higher number indicating higher quality. For each study, we assessed ASCVD incidence or prevalence. There were insufficient data to perform a meta-analysis, but the adjusted Wald method was used to calculate incident and prevalent ASCVD with 95% confidence intervals.

RESULTS

Literature search. Our search strategy yielded 2625 potentially relevant citations. After removing 372 duplicate citations, there were 2253 unique citations that underwent abstract review. Of 138 publications that underwent full text review, 21 met inclusion criteria. Several cohorts (Rochester Epidemiology Project [REP], Veterans Affairs Rheumatoid Arthritis [VARA], the Consortium of Rheumatology Researchers of North America [CORRONA], the National Data Bank for Rheumatic Diseases [NDB], Outcome of Rheumatoid Arthritis Longitudinal Evaluation [ORALE], Geisinger, Pima) resulted in numerous publications with similar cohorts, thus the largest and most recent study for each cohort was selected. In addition, studies that did not report

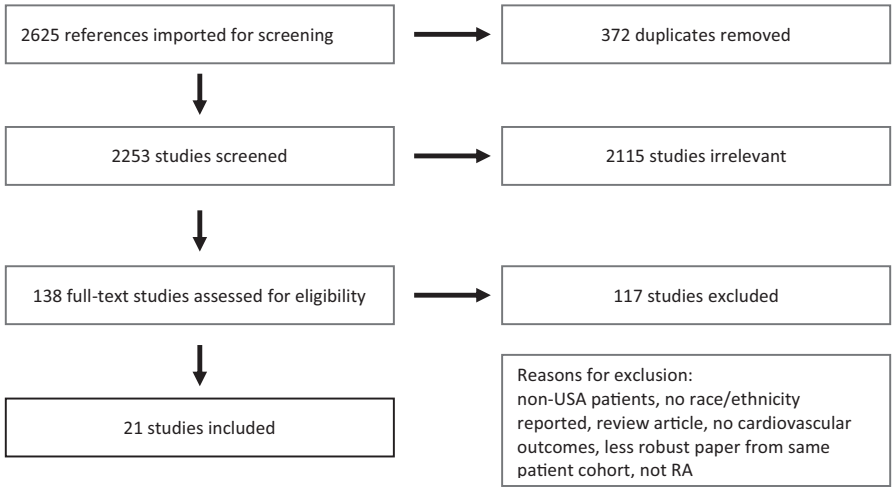

Figure 1. PRISMA Diagram

race/ethnicity data were excluded at the full text stage. Figure 1 demonstrates study selection in a PRISMA diagram.

Study characteristics. Twenty-one studies underwent full text analysis, with a total of 1624402 patients with RA. One study reported ASCVD incidence in American Indians only, but otherwise no study initially stratified ASCVD incidence or prevalence by race/ethnicity. The data presented in Table 2 were from authors who obliged to share this additional information as well as the American Indian study. Of ASCVD incidence studies, 14 were conducted among population-based cohorts and one was conducted in a "high risk" cohort, where all patients were hospitalized. All six ASCVD prevalence studies were conducted in a population-based cohort. Outcome reporting was not standardized among studies.

ASCVD prevalence in population-based cohorts. All studies (n = 21) assessed ASCVD incidence or prevalence in cohorts that were predominately population-based (Table 1). Only 2.0% of patients (32930 out of 1624402) were diagnosed using ACR criteria. Over 95% of patients were diagnosed using billing codes. Taken together, the studies included 1156800 (71.2%) NHW individuals. Over three-fourths of studies included in this review were composed of more than 50% NHW individuals, and one-third of the studies had more than 80% NHW. Out of all available data included in this review, 73.4% were female and 78.8% were rheumatoid factor/cyclic citrullinated peptide positive. The most common ASCVD outcomes were coronary artery disease and cerebrovascular disease, but data were incomplete, and so no statistics were performed.

Six of the 21 studies examined prevalence of ASCVD, and 15 examined ASCVD incidence. The mean follow-up of patients ranged widely from 0.5 to 13.4 years. The average prevalent ASCVD is 46.9% (95% CI: 46.8-47) and the range of prevalent ASCVD is 30% to 47%. The average incident ASCVD is 8.2% (95% CI: 8.14-8.25), and the range of incident ASCVD is 1% to 46%. For available data stratified by race/ethnicity, please see Table 2. Data stratified by type of ASCVD was limited, but these data available for NHW individuals are shown in Table 3. One of the included studies provided data on the number of cases of cerebrovascular accident (CVA) and coronary artery disease (CAD) in non-NHW patients. This study evaluated 228 Hispanic patients, of whom 20 (8.8%) developed a CVA and 44 (19.3%) developed CAD. Among the 380 African American patients included in that study, 52 (13.7%) suffered a CVA and 90 (23.7%) developed CAD. Finally, out of 99 patients identified as an "other" race, 6 (6.1%) had a CVA and 34 (34.3%) developed CAD (22). Figure 2 reflects pictorially the studies who reported race/ethnicity, which were comprised of predominately NHW subjects who had lower numbers of ASCVD events. One study was conducted on all Pima Indians with the highest-incident ASCVD reported (46%). All other studies did not stratify ASCVD by race/ethnicity and are summarized in Table 1.

Quality assessment. Quality assessment of studies is provided in Supplementary Table 1. Two studies had quality scores less than 5, 7 had a score of 5 to 7, and 12 studies had quality scores more than 7. Each study had a clearly stated research question, and the study population was well defined. In all studies, the research question and outcome measures were clearly defined, valid, reliable, and implemented consistently across study participants. Confounding variables, such as ASCVD risk factors, were assessed and adjusted for in statistical analyses in 18 of 21 studies. In only 3 out of 21 studies, however, sample size justifications, power descriptions, and variance and effect estimates were given. Studies varied as to whether the exposure was assessed more than once. Six of 21 studies were cross-sectional, and the remainder were cohort or case control. Furthermore, certain checklist items did not apply to several of the included studies. Because most of the populations came

Table 1. Baseline characteristics of studies included in systematic review

Reference	*N*	Data Source	RA Case Definition	Gender (% female)	Mean Follow-up (y)	RF/CCP Positive (%)	NHWa (%)	ASCVDb (%)
Studies examining incidence of ASCVD								
Jacobsson, 1993 (32)	172	Pima reservation data	ACR criteria	54	...	...	0	46
Evans, 2011 (33)	636	ORALE cohort	ACR criteria	66	5.4	71	34	19
Solomon, 2013 (34)	22 907	SABER, Medicaid, Kaiser	ICD-9 codes + DMARD	86	0.5	...	62	1
Dave, 2014 (35)	842 787	National Inpatient Sample (1993-2007)	ICD-9 codes	75	...	...	62	8
Mikuls, 2002 (36)	158	Iowa Women's Health Study	Physician diagnosis	100	13.4	61	63	6
Al-Aly, 2011 (37)	20 811	Non-VARA VA database	ICD-9 codes + DMARD	9	3.4	...	66	44
Talabi, 2017 (38)	556	Women's Health Initiative	Chart review – CCP+ and use of DMARD	100	8.9	100	68	26
Navarro-Millan, 2016 (39)	37 568	Non-VARA VA database	ICD-9 codes + DMARD	10	4.5	69	71	4
Hassan, 2015 (40)	20 810	Single center	Patient self-report	76	...	100	73	8
Davis, 2013 (41)	1047	VARA cohort	ACR criteria	9	4.3	89	78	9
Curtis, 2017 (42)	16 796	Medicare claims	ICD-9 codes	79	...	...	84	2
Kaushik, 2015 (43)	26 042	CORRONA cohort	ACR criteria	76	3.4	77	89	2
Krishnan, 2004 (44)	3862	ARAMIS cohort	ACR criteria	76	5.8	...	89	4
Mhuircheartaigh, 2017 (45)	1171	Rochester Epidemiology Project	ACR criteria	70	10	67	93	20
Bili, 2014 (46)	2101	Geisinger	ICD-9 codes	73	3.4	63	96	3
Studies examining prevalence of ASCVD								
McFarlane, 2019 (47)	503	Inpatient discharges from two centers in New York City	ICD-9, ICD-10 codes	88	0	86.6	7.2	30
Solomon, 2006 (48)	3501	Medicare + Pharmaceutical Assistance Contract for the Elderly	ICD-9 codes + DMARD	92	2	...	25	31
Ong, 2013 (22)	1279	NHANES	Patient self-report	58	10	0	45	40
Paudyal, 2020 (49)	407	United States Renal Data System	ICD-9 codes	71	...	...	63	46
Li, 2017 (50)	596 753	2010-2015 Medicare sample data	ICD-9, ICD-10 codes	76	...	...	83	47
Wolfe, 2012 (51)	24 535	National Data Bank for Rheumatic Diseases	Physician diagnosis	88	12.3	...	90	...

Note. The table is organized in ascending order of percent NHW. Data have been ascribed to race/ethnicity categories where available. Where not available, denoted with ellipses. Abbreviations: ACR, American College of Rheumatology; ARAMIS, arthritis, rheumatism, and aging medical information system; ASCVD, atherosclerotic cardiovascular disease; CCP, anticyclic citrullinated peptide; CORRONA, the Consortium of Rheumatology Researchers of North America; DMARD, disease-modifying antirheumatic disease; ICD, International Classification of Diseases; *N*, total number of patients in study; NHANES, National Health and Nutrition Examination Survey; NHW, non-Hispanic white; ORALE, Outcome of Rheumatoid Arthritis Longitudinal Evaluation; RA, rheumatoid arthritis; RF, rheumatoid factor; SABER: the safety assessment of biologic therapy; VA, veterans affairs; VARA, veterans affairs rheumatoid arthritis.
[a] Percent of NHW in entire population.
[b] Percent of ASCVD in entire population.

Table 2. Studies stratifying ASCVD by race/ethnicity in RA

Author, Year	*N*	Mean Follow-up (y)	Proportion ASCVD (%)	NHW With ASCVD (%)	Hispanic With ASCVD (%)	African American With ASCVD (%)	Other With ASCVD (%)
Jacobbson, 1993 (32)	172	...	46	...	...	...	46 (79/172)
Davis, 2013 (41)	1047	4.25	9	10 (79/819)	9 (4/47)	7 (12/161)	10 (2/21)
Ong, 2013 (22)	1279	10	40	47 (271/572)	28 (64/228)	37 (142/380)	40 (40/99)

Note. Data not available are denoted with ellipses. Abbreviations: ASCVD, atherosclerotic cardiovascular disease; *N*, total number of patients in study; NHW, non-Hispanic white; RA, rheumatoid arthritis.

from registries in which patients already agreed to participate or insurance claims databases that were de-identified and did not require consent, the participation rate was irrelevant. In addition, many of these studies did not address whether outcome assessors were blinded to the exposure status of participants, possibly because the assessments were automated and without subjectivity. Additionally, 18 out of 21 studies did not address loss to follow-up.

DISCUSSION

In this systematic review, we found that over three-fourths of studies involved over 50% NHW, and no study reported ASCVD outcome data stratified by race or ethnic minority. It is difficult to assert any trends based on the paucity of data presented, but the data do support a need for increased recruitment and reporting on ethnically diverse populations. Given heterogeneity in mean follow-up time, RA duration, race/ethnicity data, and lack of medication information, a meta-analysis was not possible. This review demonstrates that more studies are required to ascertain whether certain race/ethnic groups with RA have increased risk for developing ASCVD.

Because ASCVD is the leading cause of mortality in RA, the absence of studies reporting ASCVD cases stratified by race/ethnicity is an important gap in the literature. A recent systematic review has shown that ethnic minorities are underrepresented in trials on RA, which is consistent with the findings of our present study (23). Figure 2 suggests that as the proportion of NHWs in the population increases, the prevalence or incidence of ASCVD decreases. The preponderance of the studies included in this review had a majority of NHWs and would suggest that studies with a larger proportion of other race/ethnicities may have higher rates of ASCVD. This adds to the importance of stratifying race/ethnicity in studies of disease outcomes in RA. Ascertaining whether certain races/ethnicities with RA carry a larger ASCVD burden would facilitate earlier disease recognition as well as initiation of earlier preventive care.

Interestingly, the incidence and prevalence of ASCVD across all studies was unexpectedly low, which is likely partially due to relatively short follow-up periods. Of note, one study consisted of over 80% of the entire population in this review, and they only showed an 8% incidence of ASCVD. This study used a limited number of billing codes to identify ASCVD cases in hospitalized RA patients, calling into question whether using billing codes accurately captures the burden of ASCVD. Six of the 21 studies did not cite mean follow-up. Perhaps this is because most studies were population-based or part of a registry devised for other purposes. In data generalizable to the entire US population, between 2013 and 2016, cardiovascular disease prevalence ranged from 42.6% for Hispanic females to 60.1% for non-Hispanic African American males (24). All in all, the studies identified by the search strategy for this review demonstrated a lower incidence or prevalence of ASCVD than anticipated.

Given the limited data on ASCVD stratified by race or ethnicity, it is worth noting the relationship between seropositivity and ASCVD. Over three-quarters of patients studied were seropositive. It has been shown that seropositivity increases the prevalence of cardiovascular disease in RA (25,26). However, one large study from the Women's Health Initiative found no association (27). Future studies should continue to document RA features like seropositivity as these may be important risk factors for ASCVD.

Socioeconomic and cultural differences between NHWs and other ethnicities may also contribute to different rates of ASCVD in non-NHW patients with RA. The Hispanic paradox is where Hispanics have a high burden of ASCVD risk factors but have similar or lower rates of ASCVD compared with NHW (18). This phenomenon has been accounted for by several sociocultural theories. One observation is that Hispanics return to their country of origin when they become ill, so death rates are undercounted (28). Another is that immigration self-selects individuals who are

Table 3. Studies stratifying type of ASCVD in non-Hispanic whites with RA

Author, Year	*N*	CVA cases (*n*)	CAD cases (*n*)	PAD cases (*n*)	Carotid stenosis (*n*)	CV mortality (*n*)
Mhuircheartaigh, 2017 (45)	1034	...	202	...	...	...
Ong, 2013 (22)	1279	53	218	...	...	...
Bili, 2014 (46)	2101	14	46	8	3	4

Note. Data not available are denoted with ellipses. Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CV, cardiovascular mortality; CVA, cerebrovascular accident; *N*, total number of patients in study; *n*, number of cases; PAD, peripheral arterial disease; RA, rheumatoid arthritis.

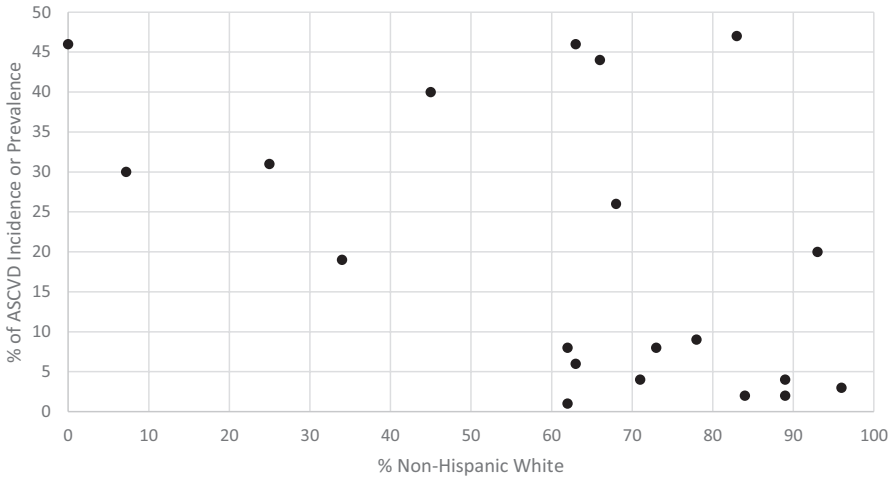

Figure 2. Percent of ASCVD incidence or prevalence relative to percent non-Hispanic whites with RA

inherently healthier and hardier in order to make the journey (29). However, more studies are needed to precisely determine what processes lead to different degrees of ASCVD among ethnicities. In addition, Hispanics and African Americans with RA have demonstrated decreased adherence to medications compared with NHWs, which may also increase ASCVD prevalence in these populations (30). Of note, these data were collected in socioeconomically disadvantaged populations. In addition, evidence has shown different predilections for engaging in complementary and alternative medicine in NHW, African Americans, or Hispanics (31). Because of the interplay of socioeconomic status, differential use of complementary and alternative medicine, and migration in and out of the United States, it is hard to ascertain specific etiologies responsible for observed racial/ethnic health disparities. Furthermore, it is difficult to extricate disparities due to socioeconomic status when examining racial/ethnic differences. Lower education and income lead to other factors such as decreased access to private insurance and preventive care that manifests in worse health outcomes. In summary, further studies are needed to characterize relative contributions of social and environmental factors responsible for racial/ethnic disparities in ASCVD within the RA population.

From a broader research agenda, incidence and prevalence may not be the correct measure to use to examine ASCVD burden. Instead, it is possible that disparities exist in ASCVD severity and prognosis rather than ASCVD incidence/prevalence in racial/ethnic minorities with RA. Again, however, future RA studies need to include more diverse populations to better assess the presence and degree of ethnic disparities in ASCVD. This systematic review demonstrates the need to collect data on disease severity, outcomes in RA, and stratify ASCVD by race/ethnicity in an ethnically diverse but socioeconomically homogeneous population.

There are several limitations related to capturing race/ethnicity data. First, data on multiethnic populations may not be accurately collected as respondents may be asked to choose one category and may therefore skew the data set. Furthermore, as previously noted, race/ethnicity are inextricably linked to socioeconomic status, and we were not able to evaluate this interplay in greater detail. As far as studies that only reported the prevalence among NHW, it is unclear how much ASCVD prevalence can be ascribed to NHW versus other race/ethnicities. Additionally, this review ascertains racial/ethnic differences in ASCVD within the United States to study patients in a relatively similar environment, which may limit extrapolation to a non-US population.

There were several limitations regarding the design of the studies included in this review. The use of incidence more often than prevalence likely plays a large role in the lower rates of ASCVD in RA seen in this review. Other key factors include duration of follow-up, time to diagnosis of RA, duration of RA, and seropositivity. Cross-sectional study design (3 of 21 studies) precludes the ability to distinguish prevalent ASCVD before a diagnosis of RA versus incident ASCVD following a diagnosis of RA. Cross-sectional studies also impair the ability to measure the accumulation of ASCVD over time as there is no follow-up reporting. In addition, there could be misclassification with ASCVD outcomes as well as RA diagnosis. Regarding ASCVD outcomes, there were limitations in our attempts to incorporate only atherosclerotic-driven cardiovascular disease; for instance, we accepted studies assessing simply "stroke," although some may have been hemorrhagic. RA was defined by ACR criteria in a small minority of cases (2.0% as mentioned above) and by ICD-9 criteria in over 95% of patients, which were not manually adjudicated. This calls into question the validity of RA diagnoses in this review. Several publications analyzed large administrative or claims databases (eg, Nationwide Inpatient Sample, National Health and Nutrition Examination Survey), which introduces the risk of ascertainment bias due to inherent limitations of these databases, including reporting self-diagnoses of RA, missing or incomplete race/ethnicity data, and missing or incomplete data on diagnosis of ASCVD.

In conclusion, this systematic review calls for the need to stratify ASCVD prevalence by race/ethnicity in RA. We have shown that many population-based studies on ASCVD prevalence in RA have been done in majority Caucasian populations. As the United States population reflects an increasing percentage of minorities, more studies must be conducted in racially/ethnically diverse populations to properly inform physicians. Furthermore, we ensured that our nomenclature in the manuscript reflects "race/ethnicity." In addition, this review calls for future studies to better understand the mechanisms underlying potential differences in ASCVD prevalence in diverse populations. Such data would enable more timely and appropriate identification and prevention of atherosclerotic cardiovascular events in the ethnically diverse RA population.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for intellectual content. All authors approved the final version to be published.

Study conception and design. Daniel, Makris, Caplan, Davis, Solow.
Acquisition of data. Daniel, Davila, Makris, Solow.
Analysis and interpretation of data. Daniel, Solow.

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