



Prevalence of lower extremity peripheral arterial disease in individuals with chronic immune mediated inflammatory disorders



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ABSTRACT

Objective: To compare the prevalence of lower extremity peripheral artery disease (PAD) and to assess whether age-associated progression in ankle-brachial index (ABI) differs between individuals with chronic immune-mediated inflammatory diseases (CIID) and the general population.

Methods: Pooled analysis with data from individuals aged 50 years and older with ABI measurements, obtained from population-based cross-sectional studies conducted in Catalonia (Spain). Information on three CIID diagnoses (i.e., inflammatory bowel disease, systemic connective tissue disorders, and inflammatory polyarthropathies and spondylopathies, considered as one entity for purposes of analysis) was obtained from electronic medical records. To ascertain the statistical association between PAD and CIID, logistic regression models were fitted and adjusted for age, sex, and cardiovascular risk factors. We tested the interaction between age and CIID diagnosis for ABI values.

Results: We included 8799 individuals, 312 (3.6%) with CIID. The age-standardized prevalence of PAD was higher in the CIID group (12% vs. 6% in general population, $p = 0.001$), and the model adjusted for age, sex, and cardiovascular risk factors also showed higher risk in individuals with CIID [Odds Ratio (95% confidence interval) = 1.65 (1.15–2.38); $p = 0.007$]. The inflammatory polyarthropathies/spondylopathies diagnosis was significantly associated with PAD in the fully adjusted model [1.80 (1.18–2.75); $p = 0.006$]. The atherosclerotic process was accelerated in individuals with CIID, compared to the general population (p for interaction < 0.001).

Conclusion: In individuals with CIID, age-standardized prevalence of PAD was significantly higher than in the general population and the atherosclerotic process was accelerated. However, only inflammatory polyarthropathies/spondylopathies was associated with significant risk of PAD.

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1. Introduction

Inflammation plays a key role in coronary artery disease and other manifestations of atherosclerosis [1]. The premature

atherosclerosis observed in chronic immune mediated inflammatory disorders (CIID) may be a consequence of the chronic inflammation inherent to these disorders [2,3]. Due to the long asymptomatic induction period of atherosclerosis, subclinical indicators of lower extremity peripheral artery disease (PAD), such as ankle-brachial index (ABI), can provide early risk detection [4,5]. In addition, pathological ABI is a strong predictor of future cardiovascular events [6].

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PAD is relatively frequent in general population in western countries [7–9] and the prevalence increased an alarming 13.1% from 2000 to 2010 [10]. Several reports have shown higher prevalence of PAD in individuals with CIID (e.g., systemic lupus erythematosus [11], rheumatoid arthritis [12], or inflammatory bowel diseases [13]). However, these studies have a modest sample size, participants have usually been recruited in-hospital, and therefore the patients are more likely to have advanced disease stages. In contrast, a population-based sample that includes individuals in a wide range of disease severity and consistently uses the same non-exposed population would enable a more accurate assessment of the prevalence of PAD associated with CIID.

The objectives of the study were: (1) To determine in individuals aged 50 years and older whether the prevalence of PAD in patients with CIID is higher than in the general population and (2) to assess whether age-associated ABI progression differs between individuals with and without CIID.

2. Methods

2.1. Design and data sources

We carried out a pooled analysis of individual data obtained from two large, population-based, cross-sectional projects that included ABI measures: REGICOR (Girona Heart Registry [Registre Gironí del Cor]) and PERART (Peripheral Artery Disease Study) [7,8]. The REGICOR project is comprised of three cross-sectional studies carried out in 1995, 2000, and 2005 in Girona Province (Catalonia, Northeast Spain), which has a population of approximately 674,000 [14]. For the present analysis, we used data from the 2005 study and from the 2010 follow-up examination of the cohorts recruited in 1995 and 2000 [15]. The PERART study selected a sample from patients attending 28 primary healthcare centers within the metropolitan area of the City of Barcelona and the county of Barcelonès Nord-Maresme between 2006 and 2008. These urban and semi-rural centers cover a population of approximately 600,000 inhabitants [16]. Both studies used similar methodology [17]. All participants were duly informed and signed their consent to participate in the studies, which were approved by the local ethics committees.

The protocol of the present study, which selected REGICOR and PERART participants aged 50 years and older, was approved by the local ethics committee (CEIC-PSMAR).

2.2. Ankle-brachial index measurement

In accordance with current guidelines [6], after 5-min rest we measured systolic blood pressure in the brachial artery in the antecubital fossa in the control arm with a continuous Doppler device, then in the distal calf, using the Doppler probe to determine systolic blood pressure in the supine position at the right and left posterior and anterior tibial arteries. Right and left ABI were calculated as the ratio of the higher of 2 systolic pressures in the lower limbs (posterior and anterior tibial arteries) to the control brachial systolic pressures. The lower of the values obtained was used for analysis. Individuals with $ABI \geq 1.4$ were excluded from the evaluation because the possible influence of arterial wall stiffness made it impossible to discard arterial obstruction. PAD was considered when an individual presented with $ABI < 0.9$.

2.3. Chronic immune-mediated inflammatory disorders

The diagnosis of CIID was obtained from the System for the Development of Research in Primary Care (SIDIAP) database, which includes the anonymized electronic medical records of

approximately 80% of the Catalan population [18]. These diagnoses were coded according to the International Classification of Diseases 10th edition (ICD-10) and divided in four groups: (1) inflammatory bowel diseases, (2) inflammatory polyarthropathies, (3) systemic connective tissue disorders, and (4) spondylopathies (Table 1). We considered inflammatory polyarthropathies and spondylopathies as a single group since both pathologies mainly present with joint damage and share the recommendations for cardiovascular risk prevention [19].

2.4. Other measurements

The PERART and REGICOR questionnaires were based on standardized World Health Organization (WHO) surveys [17,20]. Sociodemographic variables and data on tobacco use, history and treatments for hypertension, dyslipidemia, and diabetes and history of cardiovascular disease (e.g. myocardial infarction, angina, stroke, and intermittent claudication) were recorded. Anthropometric measures were collected by physical examination. Claudication was assessed using the Edinburgh questionnaire [21]. Symptomatic PAD was considered when an individual presented with $ABI < 0.9$ and claudication.

Fasting (>10 h) blood samples were analyzed in local laboratories that satisfied external quality-control requirements [8,14]. Triglycerides, glucose, total cholesterol, high density lipoprotein (HDL) cholesterol were measured by standard methods. When triglycerides were < 300 mg/dL, low density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula.

Cardiovascular risk in participants with no history of cardiovascular disease was calculated by the Framingham-REGICOR (Girona Heart Registry [Registre Gironí del Cor]) function validated for the Spanish population [22]. In addition, the REASON risk score to select candidates for screening of PAD with ABI was estimated in all participants [23].

2.5. Statistical analysis

Continuous variables were summarized as mean and standard

Table 1

Chronic immune mediated inflammatory disorders diagnoses included in each group.

ICD-10 code	Title
K50–K52	Noninfective enteritis and colitis
K50	Crohn disease (regional enteritis)
K51	Ulcerative colitis
K52	Other noninfective gastroenteritis and colitis
M05–M14, L40.5	Inflammatory polyarthropathies
M05	Seropositive rheumatoid arthritis
M06	Other rheumatoid arthritis
M07	Psoriatic and enteropathic arthropathies
M08	Juvenile arthritis
M09	Juvenile arthritis in diseases classified elsewhere
M10	Gout
M11	Other crystal arthropathies
M12	Other specific arthropathies
M13	Other arthritis
L40.5	Arthropathic psoriasis
M30–M35, G635	Systemic connective tissue disorders
M30	Polyarteritis nodosa and related conditions
M31	Other necrotizing vasculopathies
M32	Systemic lupus erythematosus
M33	Dermatopolymyositis
M34	Systemic sclerosis
M35	Other systemic involvement of connective tissue
G63.5	Polyneuropathy in systemic connective tissue disorders
M45–M46	Spondylopathies
M45	Ankylosing spondylitis
M46	Other inflammatory spondylopathies

deviation, and categorical variables as proportions. Chi-square tests for categorical variables and ANOVA and Student t test for continuous variables were computed to test differences in the prevalence of PAD, sociodemographic variables, co-morbidity, and cardiovascular risk factors prevalence, stratified by disease group (inflammatory polyarthropathies and spondylopathies, systemic connective tissue disorders, and inflammatory bowel diseases) and by the presence of PAD.

The prevalence of PAD and of symptomatic PAD was standardized to the age distribution of the European population [24]. To assess the association between the prevalence of PAD and the diagnosis of CIID, logistic regression models of increasing complexity were fitted, adjusting for confounders that were significantly associated with both variables. The analysis included all individuals with CIID, stratified by disease group. A sensitivity analysis was performed for the group of inflammatory polyarthropathies, excluding individuals with spondylopathies. Additionally, to assess the association between the prevalence of PAD and the diagnosis of CIID in individuals with ABI ≥ 1.4 , we adjusted a logistic model comparing these participants with those with normal ABI values (≥ 0.9 and < 1.4).

Finally, we estimated the Pearson correlation between ABI and age and the interaction between age and ABI values for CIID diagnosis in a linear regression model.

3. Results

We included 8799 individuals in our analysis, 3501 (39.8%) from the PERART Study and 5298 (60.2%) from the REGICOR Study, 4697 (53.4%) women, mean age 64 years (standard deviation = 9). Inflammatory polyarthropathies was the most prevalent CIID diagnosis in both population-based studies (2.4%), followed by inflammatory bowel disease (0.6%), systemic connective tissue disorders (0.5%) and spondylopathies (0.2%) (Supplementary Table 1).

Age-standardized PAD prevalence was significantly higher in individuals diagnosed with CIID compared to those without CIID, but there was no difference in the prevalence of symptomatic PAD (Fig. 1). In addition, individuals with CIID were significantly older, more often presented with hypertension, diabetes, history of cardiovascular disease and PAD, and had significantly higher waist circumference, greater 10-year cardiovascular risk, and lower ABI. Individuals with CIID were also more frequently under

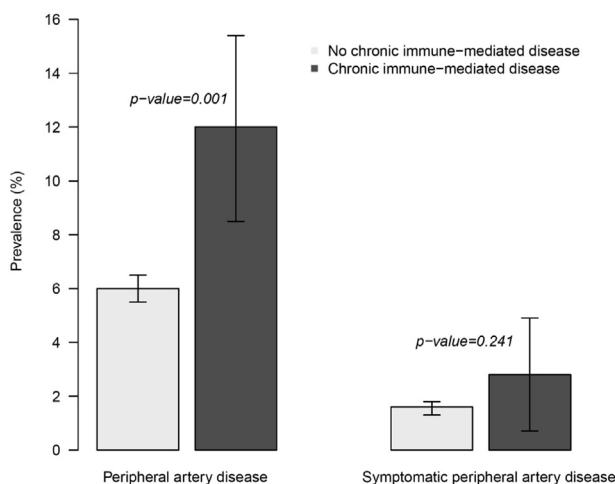


Fig. 1. Prevalence of overall and symptomatic peripheral artery disease adjusted by European population [26].

treatment for hypertension or dyslipidemia. Finally, individuals with CIID were more likely to be selected for PAD screening with ABI, according to REASON estimates, than those without (Table 2). The prevalence of cardiovascular risk factors in individuals with and without PAD has been included in Supplementary Table 2.

The diagnosis of CIID significantly increased the risk of PAD in the model adjusted for age and sex and in the fully adjusted model (Table 3). In the stratified analysis, inflammatory polyarthropathies/spondylopathies was the only group of disorders significantly associated with PAD in both models. We performed a sensitivity analysis for individuals with inflammatory polyarthropathies, with similar results. The odds ratios for systemic connective tissue disorders or inflammatory bowel diseases were ≥ 1.5 in all instances but did not reach significance (Table 4). On the other hand, individuals with CIID did not present with higher risk of having ABI ≥ 1.4 than the general population (Supplementary Table 3).

Finally, age and ABI showed a significant inverse association in individuals with and without CIID, although this association was stronger in individuals with CIID. In addition, the interaction between age and ABI was statistically significant (p -value < 0.001) for CIID diagnosis (Fig. 2).

4. Discussion

The results of this population-based analysis showed an age-associated increase in risk of PAD and lower ABI in patients with CIID, compared with the general population. However, inflammatory polyarthropathies/spondylopathies was the only group of disorders that showed an additional risk of PAD not explained by classical cardiovascular risk factors. On the other hand, the magnitude of the association between systemic connective tissue disorders or inflammatory bowel diseases and PAD may suggest an association that was not significant because of the low number of individuals with these diagnoses included in the study. Nonetheless, this high PAD risk points out that individuals with CIID are a vulnerable group not only for intermittent claudication but also for other cardiovascular events such as myocardial infarction and stroke [6].

4.1. Atherosclerosis in chronic immune-mediated diseases

CIID have been associated with accelerated atherosclerosis by several mechanisms such as endothelial dysfunction or systemic inflammation, an association not explained only by the worse cardiovascular risk profile observed in previous studies [2]. Our study confirmed this observation and also showed that individuals diagnosed with CIID and with no history of cardiovascular disease had higher cardiovascular risk than the general population. These differences were particularly clear for inflammatory polyarthropathies alone and also for the combined entity that included spondylopathies. Several authors have studied the risk factors associated with PAD prevalence in individuals with rheumatoid arthritis, the most paradigmatic disease of this group [12,25–27]. The consistent conclusion was that systemic inflammation [12,26,27] and the severity of rheumatoid arthritis, measured with bone cortical thickness, were related to low ABI in these individuals [25].

Concurring with previous reports, we found a significant association between systemic connective tissue disorders and PAD that disappeared when the analysis was adjusted for age, sex, and other potential confounders or intermediate variables [28,29]. The number of individuals in our sample who were diagnosed with these disorders was likely insufficient to observe significant

Table 2
Characteristics of participants by diagnosis of chronic immune mediated disorders.

	Inflammatory polyarthropathies N = 223	Systemic connective tissue disorders N = 41	Inflammatory bowel diseases N = 48	No chronic immune mediated disorders N = 8487	p-value
Age, mean (SD)	67 (9)	70 (7)	66 (8)	64 (9)	<0.001
Sex (women), n (%)	85 (38.1)	26 (63.4)	24 (50.0)	4562 (53.8)	<0.001
Smoking status, n (%)					0.001
Non smoker	100 (44.8)	26 (65.0)	26 (54.2)	4846 (57.4)	
Former smoker	86 (38.6)	11 (27.5)	18 (37.5)	2238 (26.5)	
Smoker	37 (16.6)	3 (7.5)	4 (8.3)	1354 (16.1)	
Body mass index, mean (SD)	29.5 (4.7)	28.3 (5.0)	28.3 (3.3)	28.4 (4.6)	0.003
Waist circumference, mean (SD)	102.0 (12.5)	101.2 (9.8)	100.5 (8.2)	96.9 (12.4)	<0.001
Systolic blood pressure (mmHg), mean (SD)	140 (20)	137 (21)	133 (17)	136 (20)	0.012
Diastolic blood pressure (mmHg), mean (SD)	80 (10)	77 (11)	77 (10)	80 (10)	0.083
Hypertension, n (%)	168 (75.3)	30 (73.2)	33 (68.8)	5395 (64.0)	0.003
Treated hypertension ^a , n (%)	114 (68.3)	23 (79.3)	25 (80.6)	2926 (54.9)	<0.001
Total cholesterol (mg/dl), mean (SD)	209 (39)	206 (30)	216 (42)	216 (41)	0.029
HDL cholesterol (mg/dl), mean (SD)	52 (14)	59 (18)	53 (12)	54 (14)	0.009
LDL cholesterol (mg/dl), mean (SD)	130 (35)	123 (27)	140 (36)	138 (35)	0.001
Triglycerides (mg/dl), median [interquartile range]	115 [85–154]	109 [88–138]	115 [89–142]	102 [76–140]	0.002
Dyslipidemia, n (%)	118 (52.9)	19 (46.3)	30 (63.8)	4105 (48.6)	0.112
Treated dyslipidemia ^b , n (%)	68 (58.1)	14 (73.7)	16 (53.3)	1973 (48.6)	0.029
Glycaemia (mg/dl), median [interquartile range]	99 [92–110]	103 [89–119]	97 [90–109]	97 [89–108]	0.083
Diabetes, n (%)	55 (24.7)	16 (39.0)	16 (33.3)	1773 (20.9)	0.003
Treated diabetes ^c , n (%)	30 (54.5)	8 (50.0)	5 (31.2)	808 (46.1)	0.381
Anti-platelet or anticoagulant drugs, n (%)	56 (25.5)	12 (30.0)	7 (14.6)	1712 (20.5)	0.094
10-year cardiovascular risk ^d , median [interquartile range]	5.7 [3.8–9.2]	5.1 [2.4–9.2]	4.5 [3.1–7.0]	4.2 [2.6–7.2]	<0.001
REASON risk score $\geq 4.1\%$ ^e , n (%)	136 (75.6)	31 (88.6)	35 (81.4)	4745 (63.2)	<0.001
History of cardiovascular disease, n (%)	35 (15.7)	4 (9.8)	5 (10.4)	681 (8.0)	0.001
Ankle-brachial index, mean (SD)	1.05 (0.17)	1.03 (0.17)	1.04 (0.15)	1.07 (0.13)	0.003
Peripheral artery disease, n (%)	30 (13.5)	6 (14.6)	5 (10.4)	531 (6.3)	<0.001
Symptomatic peripheral artery disease, n (%)	7 (3.3)	1 (2.6)	0 (0.0)	127 (1.5)	0.146

^a In individuals diagnosed with hypertension.

^b In individuals diagnosed with dyslipidemia.

^c In individuals diagnosed with diabetes.

^d In individuals aged 50 to 74 and with no history of cardiovascular disease.

^e In individuals aged 50 to 79 and with no history of cardiovascular disease. HDL: High-density lipoprotein. LDL: Low-density lipoprotein. SD: Standard deviation.

Table 3
Adjusted odds ratio of peripheral artery disease (ankle brachial index <0.9 in population with ankle brachial index <1.4) for chronic immune mediated disorders.

	Peripheral artery disease			
	Model 1		Model 2	
	OR (95% CI)	p	OR (95% CI)	p
Chronic immune mediated inflammatory disorder	1.79 (1.26–2.54)	0.001	1.65 (1.15–2.38)	0.007
Age	1.09 (1.07–1.10)	<0.001	1.08 (1.07–1.09)	<0.001
Sex (ref. men)	0.59 (0.50–0.70)	<0.001	1.09 (0.85–1.40)	0.482
Former smoker	–	–	1.88 (1.44–2.46)	<0.001
Current smoker	–	–	3.41 (2.55–4.56)	<0.001
History of cardiovascular disease	–	–	2.27 (1.81–2.86)	<0.001
Body mass index	–	–	0.98 (0.96–1.00)	0.044
Hypertension	–	–	1.69 (1.33–2.14)	<0.001
Diabetes	–	–	1.45 (1.19–1.77)	<0.001
Dyslipidemia	–	–	1.28 (1.06–1.54)	0.009

Model 1 has been adjusted for age and sex. Model 2 has been adjusted for age, sex, smoking status, history of cardiovascular disease, body mass index, hypertension, diabetes, and dyslipidemia.

differences. Nonetheless, several authors have pointed out that PAD predicted the likelihood of more severe systemic lupus erythematosus activity, the most frequent disease in this group, or more widespread atherosclerotic disease [11,28].

Finally, our study did not find a significant association between inflammatory bowel disease and PAD in the adjusted models. This finding concurs with a recently published meta-analysis [30].

4.2. Clinical implications

Asymptomatic PAD, an early functional biomarker of atherosclerosis, places individuals at high risk for cardiovascular events [6]. The age-standardized prevalence of PAD observed in the CIID population was twice that observed in the general population aged 50 years and older (12% vs. 6%). Therefore, these individuals with

Table 4
Adjusted odds ratio of peripheral artery disease (ankle brachial index <0.9 in population with ankle brachial index <1.4), for component chronic immune-mediated disorders (i.e., inflammatory polyarthropathies and spondylopathies, systemic connective tissue disorders, inflammatory bowel diseases).

	Peripheral artery disease		Inflammatory polyarthropathies + spondylopathies		Systemic connective tissue disorders		Inflammatory bowel disease					
	Model 1		Model 2		Model 1		Model 2					
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p				
Chronic immune mediated inflammatory disorder	1.94 (1.29–2.92)	0.002	1.80 (1.18–2.75)	0.006	1.87 (0.77–4.55)	0.168	1.52 (0.57–4.09)	0.406	1.55 (0.60–4.02)	0.365	1.49 (0.56–3.95)	0.422
Age	1.09 (1.07–1.10)	<0.001	1.08 (1.07–1.09)	<0.001	1.08 (1.07–1.10)	<0.001	1.08 (1.07–1.09)	<0.001	1.08 (1.07–1.09)	<0.001	1.08 (1.07–1.09)	<0.001
Sex (ref. men)	0.59 (0.50–0.71)	<0.001	1.09 (0.85–1.39)	0.508	0.60 (0.50–0.72)	<0.001	1.11 (0.86–1.43)	0.412	0.59 (0.50–0.71)	<0.001	1.09 (0.85–1.41)	0.480
Former smoker	–	–	1.83 (1.40–2.40)	<0.001	–	–	1.86 (1.41–2.44)	<0.001	–	–	1.84 (1.40–2.42)	<0.001
Current smoker	–	–	3.36 (2.51–4.50)	<0.001	–	–	3.43 (2.55–4.61)	<0.001	–	–	3.34 (2.48–4.49)	<0.001
History of cardiovascular disease	–	–	2.20 (1.75–2.78)	<0.001	–	–	2.21 (1.74–2.81)	<0.001	–	–	2.25 (1.77–2.86)	<0.001
Body mass index	–	–	0.98 (0.95–1.00)	0.029	–	–	0.97 (0.95–0.99)	0.014	–	–	0.97 (0.95–1.00)	0.021
Hypertension	–	–	1.68 (1.32–2.14)	<0.001	–	–	1.71 (1.34–2.18)	<0.001	–	–	1.70 (1.33–2.16)	<0.001
Diabetes	–	–	1.44 (1.18–1.76)	<0.001	–	–	1.49 (1.22–1.83)	<0.001	–	–	1.46 (1.19–1.79)	<0.001
Dyslipidemia	–	–	1.29 (1.07–1.55)	0.007	–	–	1.27 (1.05–1.53)	0.014	–	–	1.26 (1.04–1.52)	0.016

Model 1 has been adjusted for age and sex. Model 2 has been adjusted for age, sex, smoking status, history of cardiovascular disease, body mass index, hypertension, diabetes and dyslipidemia.

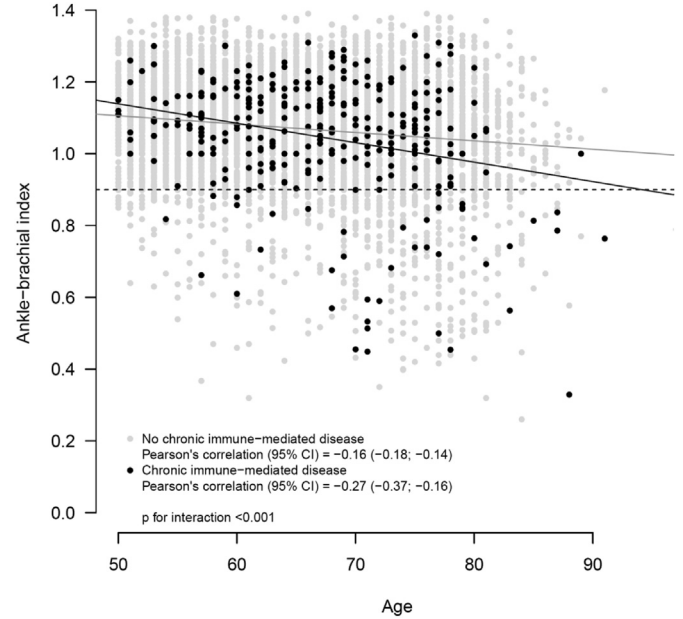


Fig. 2. Ankle-brachial index by age in individuals with and without chronic inflammatory immune mediated disorders. Dashed line indicates ankle-brachial index = 0.9.

CIID represent a vulnerable group in whom cardiovascular risk functions do not reflect actual risk [31]. In our study, individuals with CIID were more often under treatment for hypertension and dyslipidemia. In addition, the use of PAD pre-screening functions could have greater benefits in individuals with PAD, since CIID individuals presented with significantly higher REASON risk scores [4,23]. Indeed, the detection of ABI has been particularly useful after initial cardiovascular risk assessment to appropriately reclassify individuals from moderate to high risk [32].

4.3. Characteristics and limitations of the study

Our study has several limitations. First, a cross-sectional study design cannot establish causal associations. In addition, selection bias may affect any cross-sectional study; however, this effect is likely to be modest in the present study because it was population-based and participants were not selected on the basis of the presence or absence of PAD or CIID. Second, identification of lower extremity PAD was based on either claudication or an abnormal ABI (<0.9). The latter, a surrogate marker of generalized atherosclerosis, is the most commonly used test to screen PAD in clinical settings and to estimate the prevalence of the disorder in epidemiologic studies [5–9,33]. Third, it was beyond the objectives of our study to measure blood biomarkers (e.g., systemic inflammation, endothelial dysfunction, or prothrombotic state) to explore the potential mechanisms that may accelerate atherosclerosis in CIID patients [2,34]. To avoid misclassification bias, we used medical diagnosis of CIID as a robust marker of inflammatory status. These diagnoses were extracted from routinely collected databases that may contain underreporting; however, the SIDIAP database has been validated for research in cardiovascular epidemiology [35] and rheumatic diseases [36]. Indeed, the prevalence of CIID found in SIDIAP concurred with previous studies [37–39]. Finally, we grouped diagnoses in order to increase the number of exposed individuals for analysis (e.g., inflammatory polyarthropathies instead of rheumatoid arthritis). Nonetheless, we were not able to detect significant differences in two disease groups, systemic connective tissue disorders and inflammatory bowel diseases. Further cohort studies

with larger sample sizes are required to confirm the findings of the present cross-sectional study.

5. Conclusion

CIID diagnosis increases the risk of PAD. In our study, individuals diagnosed with CIID presented with higher age-adjusted prevalence of PAD and higher magnitude of association between age and ABI than the general population, suggesting an accelerated atherosclerotic process. However, the only disease group with significant risk of PAD was inflammatory polyarthropathies/spondylopathies. Individuals diagnosed with systemic connective tissue disorders and inflammatory bowel diseases showed a higher PAD prevalence that was nonsignificant after adjustment, perhaps because of the low number of individuals with these disorders included in the study.

Conflict of interest

No conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.atherosclerosis.2015.06.054>.

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