




## ORIGINAL RESEARCH

## Cardiovascular disease risk in patients with inflammatory arthritis nowadays still substantially elevated

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## ABSTRACT

**Objectives** This study aims to assess current cardiovascular disease risk and prevalence of risk factors in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (SpA).

**Methods** 2050 consecutive patients with inflammatory arthritis (IA) and 939 controls were included, with 1308 patients with RA, 356 patients with PsA and 386 patients with SpA. In a prospective cohort setting, questionnaires regarding previous cardiovascular events and risk factors were used to assess cardiovascular risk and prevalence in patients with IA by calculating ORs using logistic regression models.

**Results** 'Traditional' cardiovascular (CV) risk factors were significantly elevated in patients with IA compared with controls. Cardiovascular disease (CVD) ORs were increased in patients with RA and PsA compared with controls, 1.61 (95% CI: 1.04 to 2.48) and 2.12 (95% CI: 1.23 to 3.66), respectively, and a trend towards increased odds was observed in patients with SpA (OR 1.43; 95% CI: 0.79 to 2.59). After adjusting for traditional risk factors, CV risk was not increased in patients with RA (OR; 0.95, 95% CI: 0.58 to 1.55), PsA (OR 1.19; 95% CI: 0.64 to 2.22) and SpA (OR; 0.91, 95% CI: 0.47 to 1.77).

**Conclusion** CVD is currently still more prevalent in patients with IA compared with healthy controls and, more importantly, this elevated risk is highly influenced by an increased prevalence of 'traditional' CV risk factors. More attention to, as well as improvements in, identification and treatment of 'traditional' risk factors, need to be made for not only RA, but other IA conditions as well.

## INTRODUCTION

The worldwide prevalence of inflammatory arthritis (IA) is approximately 3%, with rheumatoid arthritis (RA), psoriatic arthritis (PsA), axial spondyloarthritis (SpA) being the most common subtypes of IA. IA is associated with an elevated risk of cardiovascular burden.<sup>1-3</sup> It has been well established that patients with RA have a higher risk of developing cardiovascular diseases (CVD) than the general population.<sup>4</sup> Also, patients with RA have an increased

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The increased cardiovascular disease risk in patients with inflammatory arthritis has diminished in recent years.

## WHAT THIS STUDY ADDS

⇒ We found that the cardiovascular risk in patients with inflammatory arthritis is still increased and is highly influenced by 'traditional' risk factors, less so by inflammation.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ All patients with inflammatory arthritis need better, structural screening for and treatment of 'traditional' cardiovascular risk factors, to attenuate their increased risk.

overall mortality, primarily due to cardiovascular (CV) events.<sup>5</sup> While the CVD risk of other inflammatory rheumatic diseases such as PsA and SpA has been disputed, and data is limited, recent research shows an increased risk compared with healthy controls, with ORs up to 1.43 and 1.97, respectively,<sup>6,7</sup> while other studies found CV morbidity similar to that in patients with RA.<sup>8-12</sup> Furthermore, a large population-based cohort recently found higher HRs for patients with ankylosing spondylitis compared with RA (1.97 vs 1.83).<sup>6</sup>

However, most guidelines do not yet recommend the same CV screening strategies for RA, PsA and SpA, despite the results of these above-mentioned studies. While the European Alliance of Associations for Rheumatology advises CV risk assessment of all patients with IA every 5 years, it advises to apply a multiplication factor of 1.5 to calculated risk scores only in patients with RA.<sup>13</sup> The European Society of Cardiology states that a multiplication factor in patients with RA should be considered depending on disease severity.<sup>14</sup>

The increased CVD risk in patients with IA is partly due to systemic inflammation as well as an increased prevalence of ‘traditional’ risk factors, such as hypertension and dyslipidaemia.<sup>15</sup> Inflammation can also affect the development of these risk factors.<sup>16</sup> In the past two decades, more efficacious anti-inflammatory treatment options have become available, that is, biological and targeted synthetic disease modifying anti-rheumatic drugs (b/tsDMARDs). Treatment with these drugs has resulted in a decreased, but still elevated, CVD risk in these patients by lowering systemic inflammation.<sup>17–19</sup> bDMARD therapy has also been shown to reduce risk of recurrent CVD in patients without IA, but with a history CVD.<sup>20</sup>

The aim of the current study was to evaluate whether the risk of developing CVD in patients with IA remains elevated compared with the general population, despite advances in anti-inflammatory therapy, in a real-world setting.

## METHODS

### Study participants

Data were derived from a prospective cohort study (Netherlands Trial Register, trial ID NL8513), that was primarily designed to compare the disease severity of COVID-19 between patients with rheumatic diseases and healthy controls.<sup>21</sup> Between April 2020 and March 2021, all adult patients with rheumatic immune-mediated inflammatory diseases (IMID) from the Amsterdam Rheumatology and Immunology Center, were asked to participate in this study. Participants were asked, but not obliged, to register an age-matched and sex-matched healthy control without a rheumatic IMID. In the current study we focused on patients with RA, PsA and SpA.

### Assessments

Demographic and clinical data were collected using a series of digital questionnaires, which were primarily focused on COVID-19. Data on patient characteristics were collected at baseline and included age, sex, height, weight, smoking status, educational level, ethnicity, type of IMID and presence of comorbidities. In all questionnaires participants were asked to report disease activity, medication use and COVID-19-related characteristics and symptoms. Disease activity was measured using patient-reported outcome measures (PROMs), including the Routine Assessment of Patient Index Data-3 and two Visual Analogue Scales, for disease activity and pain, all scored 1–10. For the present study, we included additional questions which focused on CV risk factors and CVD in the questionnaire that was distributed in January 2021. The prevalence of CV risk factors was defined as either self-reported presence of and/or medication use against a risk factor. Self-reported CVD were assessed as coronary heart disease, peripheral arterial disease or cerebral arterial disease, according to the International Statistical Classification of Diseases and related health

problems ninth revision (codes, 410.0–410.9, 435.9, 436, 443.9 and 798).

### Statistical analysis

Baseline characteristics were presented as mean±SD, median (inner quartiles) or frequencies (percentages), depending on the distribution of data. ORs of CVD in patients with IA compared with controls were calculated using logistic regression techniques. Analyses were adjusted for sex and age in model 1, and additionally for traditional risk factors of CVD, including body mass index (BMI), hypertension (self-reported or usage of antihypertensive medication), dyslipidaemia (self-reported or usage of lipid-lowering medication), diabetes mellitus (DM; self-reported or usage of antidiabetics), and smoking in model 2, and only these traditional risk factors in model 3. Full association models are shown in online supplementary table S1. All statistical analyses were performed with IBM SPSS Statistics for Windows, V.23 (IBM, Armonk, New York, USA).

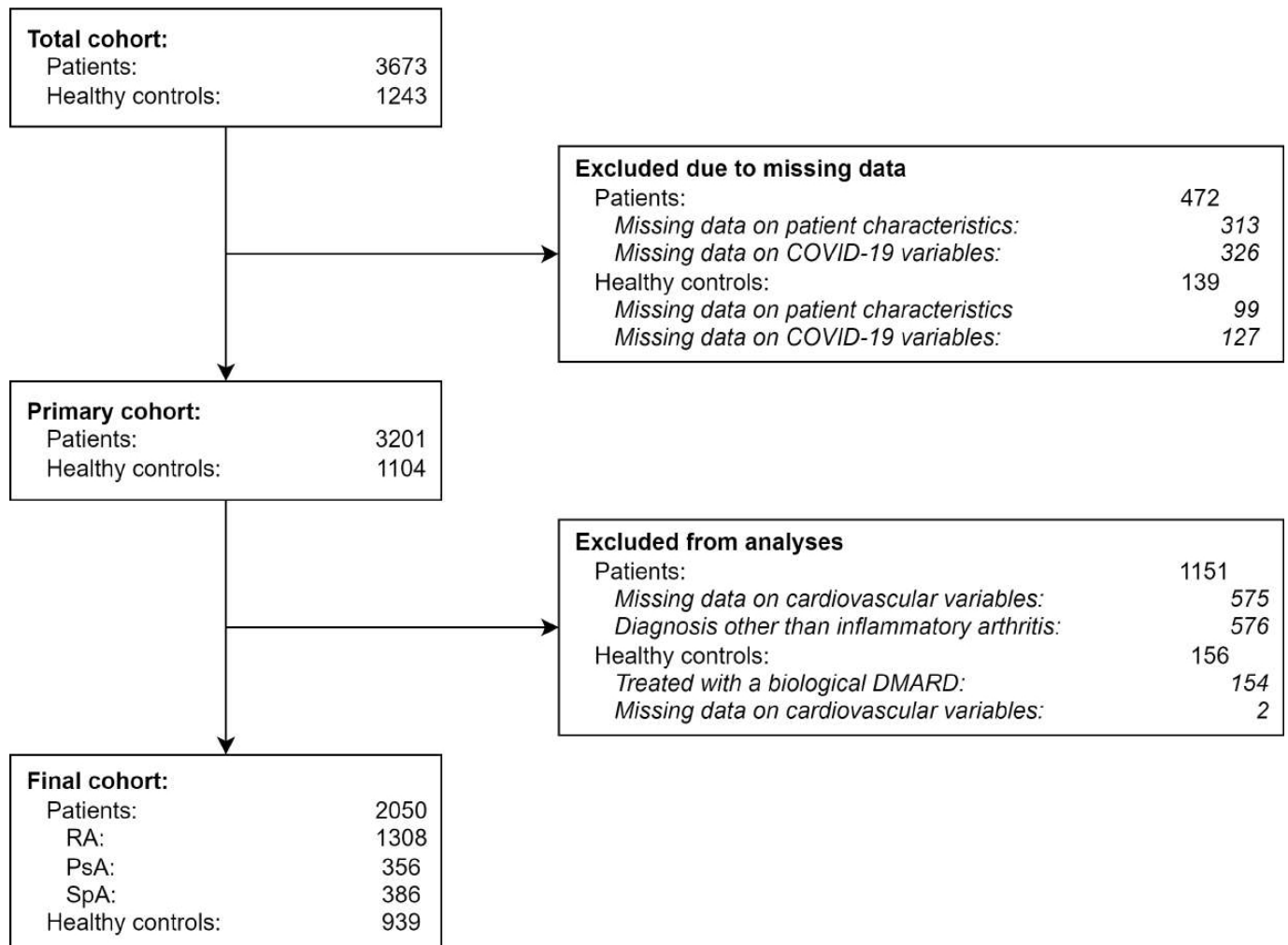
## RESULTS

### Baseline characteristics

In total, 3201 patients with rheumatic IMIDs and 1104 healthy controls received the questionnaires. After exclusion of patients without IA and participants who had not filled out the questionnaire, data was analysed from 2050 patients with IA (1308 patients with RA, 356 patients with PsA and 386 patients with SpA), and 939 healthy controls (figure 1). The mean age of patients with IA was 57±13 years compared with 55±13 years for controls. Sixty-three per cent of patients and 69% of controls were women. Median disease duration was slightly longer in patients with SpA compared with RA and PsA (15 vs 13 years), and median disease activity was slightly higher in SpA compared with RA and PsA (scored 0.5 higher in all three PROMs). Patients with SpA more often used non-steroidal anti-inflammatory drugs and used fewer conventional synthetic DMARDs (csDMARDs) than patients with RA and PsA. 39% of patients with RA used bDMARDs, compared with 47% of patients with PsA and 57% of patients with SpA. Baseline characteristics and details on current anti-rheumatic treatment are shown in table 1.

### Cardiovascular risk factors

Median BMI was significantly higher in the IA group (25.3) compared with the healthy control (24.4), with the highest BMI found in patients with PsA (26.3). Patients with IA exercised less (420 min/week for RA/PsA, 390 min/week for SpA) compared with controls who exercised 490 min/week. Thirty-four per cent of patients with RA had never smoked, compared with 38% of patients with PsA, 36% of patients with SpA and 44% of controls. A higher prevalence of hypertension (38% vs 25%), dyslipidaemia (31% vs 22%) and diabetes (5% vs 1%) was reported in patients with IA as compared with controls. Overall patients also used more antihypertensive



**Figure 1** Flow diagram of study design. DMARD, disease-modifying anti-rheumatic drug; PsA, psoriatic arthritis, RA, rheumatoid arthritis, SpA, (axial) spondyloarthritis.

(20% vs 14%), lipid-lowering medication (16% vs 10%), antidiabetic (2% vs 1%) and anticoagulant medication than controls (14% and 10%, respectively). An overview of CV risk factors is shown in [table 2](#).

### Cardiovascular disease

The number of patients with a history of CVD was higher among patients with IA (n=110; 5%) compared with healthy controls (n=31; 3%). CVD events were mainly cardiac in all groups, accounting for 69% of all events in patients with IA and 76% in controls. The odds of having CVD were 1.66 times higher in patients with IA (OR: 1.66, 95% CI: 1.11 to 2.49) compared with healthy controls. Similar findings were found for the prevalence of RA, PsA and SpA, respectively, 5%, 7% and 4%. We found that unadjusted ORs were significantly increased in RA (OR: 1.61, 95% CI: 1.04 to 2.48) and PsA (OR: 2.12, 95% CI: 1.23 to 3.66) compared with controls, while the OR in SpA did not reach statistical significance (OR: 1.43, 95% CI: 0.79 to 2.59). Adjustment for age and sex in model 1 decreased the CV risk in patients with RA and PsA, but not in patients with SpA (OR 1.49; 95% CI: 0.80 to 2.76). When additionally adjusting for ‘traditional’ CV

risk factors (age, sex, BMI, smoking, hypertension, DM and dyslipidaemia) in model 2, the CV risk decreased in all patient groups, with only the OR in PsA remaining slightly, although not significantly, increased (OR 1.19; 95% CI: 0.64 to 2.22). Adjusting solely for these ‘traditional’ risk factors in model 3 yielded similar results, with slightly higher ORs in all patient groups. Results from logistic regression analyses are shown in [table 3](#).

### DISCUSSION

In line with previous findings, our results demonstrated that patients with IA more often had ‘traditional’ CV risk factors than age-matched and sex-matched controls.<sup>22 23</sup> Patients with IA had a significantly higher prevalence of hypertension, dyslipidaemia and DM, had a greater BMI and exercised less compared with controls, and both patients with RA and SpA were more often current smokers. The systemic inflammation characteristic to all forms of IA seems to be partially responsible for the increased prevalence of hypertension, dyslipidaemia and DM.<sup>24 25</sup> Inflammation causes oxidative stress and endothelial dysfunction with subsequent vascular resistance and

**Table 1** Baseline characteristics

Patient characteristics	IA (n=2050)	RA (n=1308)	PsA (n=356)	SpA (n=386)	Controls (n=939)
Age, years	57±13	60±12	57±12	51±13	55±13
Women	1266 (63)	920 (70)	167 (47)	179 (46)	636 (69)
Disease characteristics					
Disease duration, years	13 (6–22)	12 (6–21)	13 (6–21)	15 (7–27)	n/a
PROMs (0–10)					
RAPID-3	3.0 (1.5–5.5)	3.0 (1.5–5.5)	3.0 (1.5–5.5)	3.5 (2.0–5.3)	n/a
VAS disease activity	3.0 (2.0–4.0)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	3.5 (2.0–5.0)	n/a
VAS pain	3.5 (1.5–6.0)	3.5 (1.0–6.0)	3.5 (1.0–6.0)	4.0 (2.0–6.0)	n/a
NSAIDs	450 (22)	213 (16)	60 (17)	177 (46)	18 (2)
Prednisone	202 (10)	174 (13)	18 (5)	10 (3)	n/a
DMARD	1588 (78)	1073 (82)	276 (78)	239 (62)	n/a
csDMARD	1118 (55)	900 (69)	186 (52)	32 (8)	n/a
Methotrexate	906 (44)	733 (56)	164 (46)	9 (2)	n/a
Hydroxychloroquine	225 (11)	218 (17)	7 (2)	0 (0)	n/a
Leflunomide	63 (3)	51 (4)	9 (3)	3 (1)	n/a
Sulfasalazine	120 (6)	90 (7)	11 (3)	19 (5)	n/a
Other	16 (1)	9 (1)	5 (1)	2 (1)	n/a
bDMARD	895 (44)	508 (39)	169 (47)	218 (57)	n/a
TNF-inhibitor	727 (36)	383 (29)	147 (42)	197 (51)	n/a
IL-6 inhibitor	32 (2)	32 (2)	0 (0)	0 (0)	n/a
IL-12/23 inhibitor	6 (0)	0 (0)	6 (1)	0 (0)	n/a
IL-17 inhibitor	37 (2)	0 (0)	15 (4)	22 (6)	n/a
Rituximab	48 (2)	47 (4)	0 (0)	0 (0)	n/a
Abatacept	48 (2)	46 (4)	2 (1)	0 (0)	n/a
tsDMARD	20 (1)	11 (1)	5 (1)	4 (1)	n/a
JAK-inhibitor	17 (1)	11 (1)	2 (1)	4 (1)	n/a
Apremilast	3 (0)	0 (0)	3 (1)	0 (0)	n/a

Data are reported as mean±SD, median (inner quartiles) or frequency (percentage) where appropriate.

bDMARD, biological DMARD; csDMARD, conventional synthetic DMARD; DMARD, disease-modifying anti-rheumatic drug; IA, inflammatory arthritis; IL, interleukin; JAK, janus kinase; NSAIDs, non-steroidal anti-inflammatory drugs; PROM, patient-reported outcome measure; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RAPID, Routine Assessment of Patient Index Data; SpA, (axial) spondyloarthritis; TNF, tumour necrosis factor; tsDMARD, targeted synthetic DMARD; VAS, Visual Analogue Scale.

finally hypertension.<sup>25</sup> Inflammation also induces dyslipidaemia.<sup>26–27</sup> Additionally, a higher prevalence of DM has been previously reported in all three forms of IA, with inflammation as a causal factor.<sup>28–30</sup> Inflammation in the pancreas causes  $\beta$ -cell dysfunction and apoptosis, leading to insulin deficiency and eventually DM.<sup>28</sup> The prevalence of these risk factors could be further increased by less physical activity of the patients with IA. Several studies have shown that sufficient physical activity can prevent CVD and has a favourable effect on all above-mentioned CV risk factors.<sup>31–33</sup> Physical activity is therefore recommended as an integral part of standard care for patients with IA.<sup>34</sup> Furthermore, smoking increases the chances of developing CVD, but also of IA.<sup>35</sup> The link between smoking and RA has long been established, but there is also evidence that smoking increases the incidence of

PsA and SpA.<sup>36</sup> Both patients and controls in our cohort often had untreated CV risk factors, with nearly half of both groups not receiving preventive medical treatment. While patients in our cohort are otherwise rather healthy (few smokers, relatively low BMI), they have a large cumulative (IA) disease burden. Despite improved treatment of inflammation in recent years, this might have resulted in vascular damage, hypertension and eventually CVD. Other research confirms that screening and treatment of ‘traditional’ CV risk factors remains suboptimal in many patients with IA.<sup>37–39</sup> To further decrease the prevalence of ‘traditional’ CV risk factors (and thus the incidence of CVD) we need to work towards timely control of inflammation, improve awareness of the CVD risk and provide structural CV risk screening and management in all patients with IA.

**Table 2** Traditional risk factors in patients with inflammatory arthritis compared with healthy controls

CV risk factors	IA (n=2050)	RA (n=1308)	PsA (n=356)	SpA (n=386)	Controls (n=939)
BMI	25.3 (22.8–28.4)	25.3 (22.6–28.7)	26.3 (23.5–29.4)	24.8 (23.0–27.7)	24.4 (22.1–17.7)
Smoking status					
Current, >1×/week	197 (10)	136 (10)	21 (6)	40 (10)	49 (5)
Current, <1×/week	58 (3)	31 (2)	8 (2)	19 (5)	22 (2)
Quit	925 (45)	599 (46)	166 (47)	160 (42)	379 (40)
Never	716 (35)	442 (34)	136 (38)	138 (36)	411 (44)
Alcohol					
Yes	1165 (57)	719 (55)	215 (60)	231 (60)	669 (71)
Incidental	442 (22)	288 (22)	66 (19)	88 (23)	170 (18)
Never	386 (19)	263 (20)	62 (17)	61 (16)	82 (9)
Exercise (min/week)					
<30 min/day	420 (211–720)	420 (181–740)	420 (220–660)	390 (210–653)	490 (220–660)
30–60 min/day	534 (26)	359 (27)	83 (23)	92 (24)	160 (17)
>60 min/day	535 (26)	314 (24)	103 (29)	118 (31)	247 (26)
>60 min/day	981 (48)	635 (49)	170 (48)	176 (46)	532 (57)
Hypertension					
Antihypertensives	770 (38)	496 (38)	140 (39)	134 (35)	231 (25)
Antihypertensives	411 (20)	268 (21)	80 (23)	63 (16)	131 (14)
Dyslipidaemia					
Lipid-lowering medication	641 (31)	422 (32)	110 (31)	109 (28)	207 (22)
Lipid-lowering medication	335 (16)	222 (17)	59 (17)	54 (14)	98 (10)
Diabetes mellitus					
Antidiabetics	109 (5)	67 (5)	26 (7)	16 (4)	13 (1)
Antidiabetics	46 (2)	28 (2)	10 (3)	8 (2)	6 (1)
Anticoagulants					
Anticoagulants	246 (12)	179 (14)	34 (10)	33 (9)	74 (8)

Data are reported as mean±SD, median (inner quartiles) or frequency (percentage) where appropriate.

BMI, body mass index; CV, cardiovascular ; IA, inflammatory arthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SpA, (axial) spondyloarthritis.

Moreover, we found that the prevalence of CVD was higher among patients with IA compared with controls. This enhanced risk is considered partially due to the chronic inflammation found in these patient groups, and due to the increased prevalence of ‘traditional’ risk factors. Adjusting our crude analyses for these ‘traditional’ risk factors highly attenuated the ORs for patients with IA versus healthy controls. These results suggest that the current CVD risk in patients with IA is nowadays highly influenced by the increased prevalence of these risk factors. This is in agreement with another recent study in patients with longstanding RA, where the contribution

of these risk factors on the CVD risk increased over the years.<sup>40</sup> The risk of CVD in patients with RA has similarly decreased, with the over twofold risk compared with the general population found more than 10 years ago lowering to a current increased risk of about 50–60%.<sup>22,40</sup> A possible explanation could be that current treatment of systemic inflammation has improved, while screening and treatment of ‘traditional’ risk factors remains insufficient.<sup>37,41</sup> Patients in our cohort used more bDMARDs than the overall population of patients with IA,<sup>42–44</sup> whereby treatment with tumour necrosis factor inhibitor has been shown to decrease CVD events in RA, and

**Table 3** ORs of cardiovascular diseases in patients with inflammatory arthritis compared with healthy controls

	OR (crude)	P value	OR (model 1)	P value	OR (model 2)	P value	OR (model 3)	P value
IA	1.66 (1.11 to 2.49)	0.01	1.38 (0.91 to 2.09)	0.13	0.99 (0.63 to 1.56)	0.96	1.05 (0.67 to 1.65)	0.82
RA	1.61 (1.04 to 2.48)	0.03	1.27 (0.83 to 2.01)	0.29	0.95 (0.58 to 1.55)	0.85	0.97 (0.60 to 1.57)	0.91
PsA	2.12 (1.23 to 3.66)	0.01	1.68 (0.96 to 2.96)	0.07	1.19 (0.64 to 2.22)	0.57	1.37 (0.75 to 2.52)	0.31
SpA	1.43 (0.79 to 2.59)	0.23	1.49 (0.80 to 2.76)	0.29	0.91 (0.47 to 1.77)	0.78	1.05 (0.56 to 2.00)	0.87

ORs are shown with 95% CIs. A p value of <0.05 was considered statistically significant. Model 1 was adjusted for age and sex, model 2 was adjusted for age, sex, BMI, smoking, diabetes mellitus, hypertension and dyslipidaemia, model 3 was adjusted for BMI, smoking diabetes mellitus, hypertension and dyslipidaemia.

BMI, body mass index; IA, inflammatory arthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SpA, (axial) spondyloarthritis.

possibly also PsA, patients.<sup>19 45 46</sup> However, larger studies demonstrating the long-term effect of (b)DMARDs on CVD for all patients with IA are scarce.

Interestingly, in our cohort, the prevalence of CVD in patients with PsA was higher than in patients with RA, and the OR of patients with PsA compared with healthy controls was consistently the highest in all models. While there are few comparative studies, the CVD risk for patients with RA is generally found to be equal or higher than patients with PsA.<sup>10 13</sup> A possible explanation for our findings might be that ‘traditional’ risk factors are not screened and treated as well in patients with PsA, due to lesser awareness. Thus far CVD comorbidity has been studied to a much greater extent in RA in comparison to PsA, and the guidelines regarding CVD risk in patients with RA are stricter than in patients with PsA.<sup>13</sup> Furthermore, PsA is more often associated with metabolic syndrome and truncal obesity than RA, which contributes to a pro-inflammatory state and eventually arterial stiffness and CVD.<sup>47 48</sup> Additionally, a number of pro-inflammatory cytokines are present in both PsA, metabolic syndrome and atherosclerosis, which helps explain the increased risk.<sup>49</sup>

Our study has several strengths. First, it covers a well-defined patient population with a large sample size and a diversity of patients in a prospective data collecting setting, with consistent data collection across groups. Second, patients were compared with age-matched and sex-matched controls to minimise bias. Finally, this study provides data regarding the CVD risk of the three most common inflammatory rheumatic diseases, of which there is limited data in previous studies.

A limitation of this study is that data regarding CVD were obtained by means of a self-completed questionnaire, and logistic constraints limited the collection of physical examination and laboratory data. Another limitation of this study is that data on CVD were cross-sectionally collected, which limits our ability to investigate causal pathways (ie, via mediation analyses). The relationship between IA, CV risk factors and CVD is complex, as chronic inflammation caused by IA conditions can contribute to CVD risk through a multitude of mediating factors.<sup>16</sup> Adjusting for CV risk factors eliminates some effects of chronic inflammation on CVD risk, so it should be noted that our adjusted results likely underestimate the total effect on CVD risk. Interpreting these adjusted results should be done with the complex relationship between inflammation and atherosclerosis, and the paradoxical effect of inflammation on lipid levels in mind. However, previous studies clearly demonstrated that chronic inflammation independently contributes to the development of CVD's, so we believe our adjusted results still provide valuable insights into the current magnitude of this association.<sup>50</sup>

In conclusion, CVD is currently still more prevalent in patients with IA compared with healthy controls and, more importantly, this elevated risk is highly related to an increased prevalence of ‘traditional’ CV risk factors.

Current treatments better address systemic inflammation with combinations of csDMARDs and/or b-/tsDMARDs, reducing its detrimental effects on CVD in these patient groups. However, more attention should be paid to identifying and treating ‘traditional’ CVD risk factors, not only in RA, but also in other IA conditions.

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