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## EXTENDED REPORT

Cardiovascular and selected  
comorbidities in early arthritis and  
early spondyloarthritis, a comparative  
study: results from the ESPOIR and  
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**To cite:** Gherghe AM, Dougados M, Combe B, *et al*. Cardiovascular and selected comorbidities in early arthritis and early spondyloarthritis, a comparative study: results from the ESPOIR and DESIR cohorts. *RMD Open* 2015;1:e000128. doi:10.1136/rmdopen-2015-000128

► Prepublication history and additional material is available. To view please visit the journal (<http://dx.doi.org/10.1136/rmdopen-2015-000128>).

Received 17 May 2015  
Revised 22 August 2015  
Accepted 25 August 2015



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**ABSTRACT**

**Objectives:** To investigate the prevalence of comorbidities in early rheumatoid arthritis (ERA) and early axial spondyloarthritis (ESpA) versus the general population.

**Methods:** Baseline data of 689 patients with ERA from the Etude et Suivi des Polyarthrites Indifférenciées Récentes (ESPOIR) cohort (age 48.2 ±12.1 years, symptoms duration 14.2±14.5 weeks) and 645 patients with ESpA from Devenir des Spondylarthropathies Indifférenciées Récentes (DESIR; age 32.8±8.4 years, axial symptoms duration 79.0 ±45.7 weeks) were analysed. Metabolic and cardiovascular diseases (CVD), infections and neoplasia were determined in each cohort. The prevalence (95% CI) of several comorbidities was compared with that in the French general population. For patients without CVD, the 10-year risk of developing CVD was calculated using the Framingham and SCORE equations. The heart age was calculated using the 2008 Framingham points system.

**Results:** 42% of patients with ERA and 20.3% of patients with ESpA had at least 1 comorbidity; the most common were arterial hypertension (AHT) and dyslipidaemia. AHT prevalence (95% CI) in ERA (18.2% (15.5% to 21.3%)), but not in ESpA (5.08% (3.57% to 7.14%)), was significantly increased ( $p<0.05$ ) compared with the general population (7.58%). Prevalence of tuberculosis history was higher in ERA (4.7% (3.3% to 6.6%)), and ESpA (0.99% (0.4% to 2.3%)) than in the general population (0.02%; both  $p<0.05$ ). No differences were observed in malignancies, coronary heart disease or diabetes. In ERA, among patients without a history of CVD, an intermediate to high CVD risk was found. The heart age exceeded the real age by 4.1±9.6 years in ERA and by 2.1±7.0 years in ESpA ( $p<0.001$ ).

**Conclusions:** We found an increased prevalence of AHT and tuberculosis history in ERA and ESpA, and an increased CVD risk. These results should prompt

**Key messages****What is already known about this subject?**

► Cardiovascular diseases and infections such as tuberculosis are frequently associated with established rheumatoid arthritis or with spondyloarthritis.

**What does this study add?**

► The risk of comorbidities, especially cardiovascular diseases and tuberculosis, is increased even in the early stages of arthritis, as well as after long periods of inflammation or prolonged treatment with corticosteroids or immunosuppressive drugs.

**How might this impact on clinical practice?**

► Patients at risk should be identified in order to diagnose comorbidities early and ultimately treat risk factors early.

rheumatologists to check these comorbidities early in the disease.

**INTRODUCTION**

Comorbidities are frequently associated with inflammatory rheumatic disorders such as rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA). RA has an increased standardised mortality ratio largely attributable to cardiovascular (CV) risk.<sup>1 2</sup> An increased CV mortality and incidence of CV diseases (CVD) has also been observed in AS, although less pronounced.<sup>1</sup> Chronic inflammation seems to predispose

patients with RA and AS<sup>3 4</sup> to hypertension, stroke and myocardial infarction.<sup>1</sup> However, it has not yet been clarified if the increased CV risk is already present early in the disease process.<sup>5 6</sup>

Chronic inflammation and autoimmunity are also associated with the development of malignancy.<sup>7</sup> Some authors suggest that, in patients with RA, these factors are responsible for the association with haematological cancer, the most common RA-associated malignancy. Haematological cancer has the highest standardised incidence ratio in the first 2 years after diagnosis.<sup>8</sup>

The increased risk of tuberculosis (TB) in patients with RA, AS and PsA is thought to be related to the immune disturbances caused by the disease itself, as well as to the treatment with immunosuppressive drugs,<sup>9</sup> including anti-tumour necrosis factor  $\alpha$  (anti-TNF $\alpha$ ) therapy.<sup>10</sup> Studies that investigated this risk usually included patients with established diseases or with long-term corticosteroid treatment.

While the literature is abundant in data about comorbidities in patients with established RA and AS, it is still not clear if these comorbidities develop over long periods of chronic inflammation, or if they are already present at diagnosis. The aim of our study was to determine the prevalence of several comorbidities in patients with early RA (ERA) and early spondyloarthritis (ESpA), and to compare them with prevalence rates in the general population. This will give insight into whether the prevalence of comorbidities is already increased shortly after the onset of the first symptoms, before long periods of chronic inflammation or immunosuppressive treatment. In addition, we aimed to determine the 10-year risk of developing CVD.

## METHODS

This is a cross-sectional study using the baseline data from two multicentre prospective cohorts initiated by the French Society of Rheumatology, Etude et Suivi des Polyarthrites Indifférenciées Récentes (ESPOIR) and Devenir des Spondylarthropathies Indifférenciées Récentes (DESIR).

### Patients

The ESPOIR cohort included 813 patients with early inflammatory arthritis from November 2002 to April 2005. The database for the present baseline analysis was locked on 15 December 2005. Detailed information of the study has been published previously.<sup>11</sup> Consecutive patients aged between 18 and 70 years who had a clinical diagnosis of RA or a diagnosis of undifferentiated arthritis with potential for progressing to RA, with onset during the past 6 months, were selected for recruitment. Two or more swollen joints for at least 6 weeks were required for inclusion. No previous treatment with disease-modifying antirheumatic drugs (DMARDs) or glucocorticoids was allowed.<sup>11</sup> From the ESPOIR cohort, patients fulfilling the 2010 American College of

Rheumatology (ACR)/European League Against Rheumatism (EULAR)<sup>12</sup> or the 1987 ACR classification criteria for RA<sup>13</sup> were selected for analysis (patients with ERA).

In the DESIR study (ClinicalTrials.gov identifier NCT01648907), a total of 708 consecutive patients with inflammatory back pain (IBP) were recruited between October 2007 and April 2010. The baseline database was locked on 12 December 2011. Detailed information of the study has been described elsewhere.<sup>14</sup> Briefly, patients aged over 18 and under 50 years were eligible for inclusion if they had IBP for  $\geq 3$  months but  $\leq 3$  years and symptoms suggestive of SpA according to the local investigator's assessment. Patients who had a history of any biological therapy were excluded; corticosteroid intake was permitted only in doses lower than 10 mg prednisone per day and stable for at least 4 weeks prior to recruitment.<sup>14</sup> From DESIR, only patients who fulfilled at least one classification criterion set for SpA (modified New York,<sup>15</sup> Amor criteria,<sup>16</sup> European Spondylarthropathy Study Group (ESSG)<sup>17</sup> or Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axial SpA)<sup>18</sup> were included in the analysis (patients with ESpA).

The general population data were gathered from the statistic reports of the French National Health Insurance Fund for the Employees (Caisse Nationale de L'assurance Maladie des Travailleurs Salaries, CNAMTS) for the year 2008. CNAMTS manages the health branch of the compulsory general scheme (Régime General, RG). The RG offers health coverage to almost 90% of the total French population.<sup>19 20</sup>

The French general population data were also collected from the L'Étude nationale nutrition santé (ENNS).<sup>21</sup> The ENNS was a cross-sectional survey conducted in continental France in 2006–2007, which aimed to describe the main factors of CV risk in a sample of adults (18–74 years) residing in metropolitan France in 2006.<sup>22</sup> Of the adults who participated in the survey, 2413 had clinical measures available (anthropometric examination and blood pressure (BP)).

### Data collected in ESPOIR

Demographical data, medical history and physical measurements of patients at baseline were recorded on a standard case report file (CRF). Data about comorbidities, including CVD, TB, cancers or smoking, were recorded as presence or absence. Physical examination included weight, height and BP. Biological parameters (blood count, erythrocyte sedimentation rate (ESR), C reactive protein (CRP), lipids, glucose concentrations) were measured using standard methods in the local laboratory of each participating centre.

### Data collected in DESIR

Social and demographic characteristics, medical history, and main clinical and biological variables at baseline were recorded on a standard CRF. Comorbidities, in

particular CVD, TB and malignant diseases and smoking, were evaluated as ever present or absent. The physical examination included height, weight, abdominal circumference and BP. The same biological parameters as in ESPOIR were measured locally using standard methods.

### Data collected in the French general population

The total prevalence rates of coronary heart disease (CHD), diabetes mellitus (DM), TB and malignancies in the adult population, as well as the data per gender and age groups, were extracted from the CNAMTS statistics for 2008.<sup>23</sup> Malignancies data included both lymphoma and solid malignancies.

The number of people with arterial hypertension (AHT) by gender and age groups in the French population aged 18–74 years was acquired from the ENNS survey.

### CV risk calculation

For both ESPOIR and DESIR, several CV risk markers were calculated: low-density lipoprotein level (LDL-cholesterol) was determined by the Friedewald *et al*<sup>24</sup> equation. Pulse pressure (PP; difference between systolic BP (SBP) and diastolic BP (DBP), normal  $\leq 40$  mm Hg), linked to vascular damage,<sup>25</sup> was calculated. The total cholesterol (TChol)/high-density lipoprotein (HDL)-cholesterol ratio (ideal  $\leq 3.5$ ) and the triglycerides/HDL-cholesterol ratio (ideal  $\leq 2$ ), markers of CV risk and of insulin resistance, respectively, were also calculated. Target values for traditional CV risk factors (measured on physical examination and blood tests) recommended by European Society of Cardiology (ESC) guidelines<sup>26</sup> were considered normal values; these include: BP (normal=120–129 mm Hg SBP and/or 80–84 mm Hg DBP, high normal=130–139 mm Hg SBP and/or 85–89 mm Hg DBP, AHT  $\geq 140$  mm Hg SBP and/or  $\geq 90$  mm Hg DBP), TChol (normal  $< 175$  mg/dL), LDL-cholesterol (normal  $< 100$  mg/dL).

After excluding all patients with a history of CVD (myocardial infarction, stroke or heart failure), the 10-year risk of developing CHD and the 10-year risk of general CVD (total CV events, including risk for stroke or heart failure) were calculated. This was done for each patient older than 30 years using the Framingham equations from 1998 (FRS 1998)<sup>27</sup> for CHD risk, and from 2008 (FRS 2008) for the general CVD risk.<sup>28</sup> Low 10-year risk is defined as  $< 10\%$  FRS, intermediate risk 10–20% and high risk  $\geq 20\%$ . The ‘heart age’ or the ‘vascular age’ is the age of a person with the same calculated CV risk, but whose risk factors were all within normal ranges. This was calculated using the Framingham 2008 points system.<sup>28–29</sup> Finally, the 10-year risk of fatal CVD was calculated for patients older than 40 years using the SCORE algorithms for low-risk countries.<sup>30</sup> Low-risk level is represented by  $< 1\%$  SCORE, intermediate risk 1–5% and high risk  $\geq 5\%$ . All three CV risk scores were calculated because they represent

different aspects of CV risk; for readability purposes, only FRS 2008 is presented in the main text because it represents the broadest definition of CV risk. FRS 1998 and SCORE are presented as online supplementary material.

### Statistical analysis

The Statistical Product and Service Solutions (SPSS) package V.20.0 was used for data analysis. Descriptive statistics were used to characterise the demographic data and comorbidities of patients with ERA and ES<sub>SpA</sub> at baseline. Data are presented as number (percentages, %) for qualitative variables and means ( $\pm$ SD) for continuous variables. The prevalence of several comorbidities in patients with ERA and ES<sub>SpA</sub> was compared with the prevalence in the general population by calculating age-specific and gender-specific prevalence ratios. In several age and gender groups of the studied cohorts, there were no cases, prevalence rates being thus null. Therefore, 95% CIs with continuity correction were calculated on the website <http://www.vassarstats.net/>, according to the recommended method described by Wilson.<sup>31</sup> 95% CIs were also calculated for AHT prevalence rates from the ENNS survey. The RG represented 91.64% of the total population of the metropolitan area of France in 2008; thus, it was considered to be an accurate representation of the population and 95% CIs were not calculated. If the prevalence (95% CI) of comorbidities in the studied cohorts did not overlap with the prevalence (95% CI) in the general population, they were considered significantly different ( $p < 0.05$ ).

Differences in inflammation markers (CRP and ESR) between patients with comorbidities and those without comorbidities were assessed by logistic regression adjusted for age, gender, body mass index (BMI) and lipid values.

Differences in values of traditional CV risk factors between men and women in the same cohort were assessed by independent samples t test ( $p \leq 0.05$  considered significant). For ESPOIR and DESIR patients with available CV risk scores, mean  $\pm$  SD scores per gender and 5-year age groups were calculated and assigned the corresponding level of risk. The heart age was compared with the real age of the patients in each cohort using paired samples t test.

## RESULTS

In total, 689 patients with ERA and 645 patients with ES<sub>SpA</sub> were included in the analysis. Participant characteristics, including demographic data and comorbidities, are summarised in [table 1](#).

As expected, patients with ERA were older and had a higher percentage of women. Serum inflammation markers (CRP and ESR) had higher values in patients with ERA. In total, 42.7% of the patients with ERA and 20.3% of the patients with ES<sub>SpA</sub> had at least one comorbidity at baseline. The most common comorbidities were AHT

**Table 1** Characteristics and comorbidities of the ESPOIR and DESIR cohorts

	ESPOIR (Nr=689) Patients with ERA N (%) or mean±SD	DESIR (Nr=645) Patients with ESpA N (%) or mean±SD
Male gender	161 (23.4)	304 (47.1)
Age (years)	48.2±12.1	32.8±8.4
Symptoms duration (weeks)	14.2±14.5	79.0±45.7
Alcohol use	105 (15.2)	94 (14.6)
ESR*	30.4±24.8	14.2±16.3
CRP†	22.6±33.9	9.4±15.0‡
At least one comorbidity	294 (42.7)	131 (20.3)
Arterial hypertension	125 (18.1)	33 (5.1)
Receive treatment (%)	93.6	54.5
Hypercholesterolaemia	101 (14.7)	42 (6.5)
Receive treatment (%)	69.3	2.4
Hypertriglyceridaemia	21 (3.0)	18 (2.8)
Dysthyroidism	82 (11.9)	24 (3.7)
Previous tuberculosis	32 (4.6)	6 (0.9)
Diabetes mellitus	28 (4.1)	6 (0.9)
Previous solid malignancies	24 (3.5)	3 (0.5)
Previous lymphoma	4 (0.6)	2 (0.3)
Coronary heart disease	6 (0.9)	0
Stroke	4 (0.6)	0
Peptic ulcer	35 (5)	26 (4)
Previous gastrointestinal bleeding	8 (1.2)	12 (1.9)
Hepatitis B	4 (0.6)	3 (0.5)
Hepatitis C	6 (0.9)	1 (0.2)

\*ESR normal &lt;20 mm/1 h.

†CRP normal &lt;10 mg/L (ESPOIR), &lt;6 mg/L (DESIR).

‡N=531.

CRP, C reactive protein; DESIR, Devenir des Spondylarthropathies Indifférenciées Récentes; ERA, early rheumatoid arthritis; ESpA, early axial spondyloarthritis; ESR, erythrocyte sedimentation rate; ESPOIR, Etude et Suivi des Polyarthrites Indifférenciées Récentes.

(18.1%), dyslipidaemia (17.7%), dysthyroidism (11.9%), TB (4.6%) and malignancies (4.1%) in ERA; and dyslipidaemia (9.3%), AHT (5.1%) and ulcer (4%) in ESpA.

Eighty-two (12.7%) patients with ESpA had received corticosteroids, and 87 (13.5%) had received DMARDs—sulfasalazine (44/87), methotrexate (38/87), mesalazine (3/87), leflunomide (1/87) or hydroxychloroquine (1/87)—whereas in patients with ERA, corticosteroids and DMARDs were not allowed at baseline.

AHT prevalence (95%CI) in ERA (18.2% (15.5% to 21.3%)), but not in ESpA (5.08% (3.57 to 7.14)), was significantly increased ( $p<0.05$ ) compared with the general population (7.58%; [table 2](#)).

This increase was noticeable especially in younger women (45–64 years), when CVD risk in the general population is generally low. A tendency towards an increase in prevalence compared with the general

population was also present in patients with ESpA, but the difference was significant only in women older than 45 years. The prevalence (95% CI) of TB was significantly higher in patients with ERA (4.7% (3.3% to 6.6%)) and ESpA (1.0% (0.4% to 2.3%)) than in the general population (0.02%; [table 3](#);  $p<0.05$ ). The increase was more accentuated in women than in men for both cohorts.

There were no significant differences for DM, CHD or malignancies in our cohorts compared with the general population.

In the logistic regression analysis, only CRP in ESpA was significantly higher in patients with AHT than in patients without hypertension ( $p<0.05$ ). There were no differences in CRP or ESR for other comorbidities tested, including CHD, stroke, TB, neoplasia or diabetes (data not shown).

Regarding the values of traditional CV risk factors (measured on clinical examination or blood tests), there were significant differences between men and women in each cohort ([table 4](#)).

In patients with ERA, men had higher SBP, BMI and glycaemia ( $p<0.05$ ), and lower HDL-cholesterol ( $p<0.001$ ) compared with women, whereas women had higher TChol levels compared with men ( $p<0.01$ ). Lower HDL-cholesterol in men led to higher lipid ratios compared with women. There were no significant differences between smoking, LDL-cholesterol and PP levels. In patients with ESpA, differences between genders were similar to the ones found in ESPOIR. Values of traditional CV risk factors were not only different between men and women, but were also higher than normal values; this included high normal BP and hyperlipidaemia.

There were 614 patients older than 30 years and without a diagnosis of CVD in ESPOIR and 398 in DESIR. All items necessary to calculate the Framingham 2008 score were available for 313 participants in ESPOIR and for 333 in DESIR. Distribution of the FRS 2008 per age and gender groups is shown for each cohort in [table 5](#).

Overall, 10-year CVD risk scores were low in patients with both ERA and ESpA (8.3±8.0% and 3.7±3.4%, respectively). However, when patients with ERA were divided into gender and age groups, men ≥55 years old were found to have a high risk (FRS 2008 ≥20%) of developing CVD, and women ≥60 years old an intermediate risk (FRS 2008 ≥10% and <20%). All ESpA gender and age groups had low FRS 2008 risk (FRS 2008 <10%). Details on the FRS 1998 and the SCORE distributions are available in the online supplementary file 1 and [table S1](#). The mean heart age of patients with ERA between 30 and 69 years was 53.8±15.6 years ([table 5](#)), which is 4.1±9.6 years higher than their real age ( $p<0.001$ ). A similar, although to a lesser extent, mean increase (2.1±7.0 years) was noticed in patients with ESpA ( $p<0.001$ ), resulting in a mean heart age of 39.2±8.2 years. The heart age is usually used together with the FRS 2008 for assessment of individual risk status of patients. As an example, a 50-year-old woman with ERA, who smokes, does not have

**Table 2** Prevalence (or CI 95%) of AHT in patients with ERA (ESPOIR) and ES<sub>Pa</sub> (DESIR) compared with the French general population in 2006–2008

Gender	Age groups	French general population		ESPOIR Patients with ERA		DESIR Patients with ES <sub>Pa</sub>	
		N	Prevalence (95% CI) (%)	N	95% CI (%)	N	95% CI (%)
Men	18–34	5	2.16 (0.80 to 5.25)	0	0 to 21.88	2	0.18 to 4.07
	35–44	6	3.66 (1.50 to 8.15)	0	0 to 14.13	8	4.98 to 20.22
	45–54	24	11.32 (7.53 to 16.56)	9	9.65 to 33.73	6	7.39 to 35.17
	55–64	24	17.78 (11.90 to 25.50)	19	24.47 to 51.94	–	–
	65–74	31	32.29 (23.31 to 42.71)	5	12.99 to 61.31	–	–
Women	18–34	2	0.53 (0.09 to 2.12)	1	0.06 to 6.83	3	0.42 to 5.02
	35–44	4	1.52 (0.49 to 4.11)	5	1.84 to 11.72	7	2.72 to 12.69
	45–54	9	2.39 (1.17 to 4.75)	19	7.49 to 18.17	7	7.00 to 30.07
	55–64	29	12.55 (8.70 to 17.69)	52	28.19 to 44.29	–	–
	65–74	38	20.65 (15.19 to 27.36)	15	30.56 to 64.67	–	–
Total		172	7.58 (6.54 to 8.77)	125	18.14 (15.37 to 21.27)	33	5.08 (3.57 to 7.14)

N, number with a diagnosis of AHT in each gender and age group.

AHT, arterial hypertension; DESIR, Devenir des Spondylarthropathies Indifférenciées Récentes; ERA, early rheumatoid arthritis; ES<sub>Pa</sub>, early axial spondyloarthritis; ESPOIR, Etude et Suivi des Polyarthrites Indifférenciées Récentes.

diabetes, has an SBP of 130 mm Hg and a TChol level of 259 mg/dL, with HDL-cholesterol of 89 mg/dL, has a calculated Framingham 2008 risk of 7.5% (low risk). However, this corresponds to a heart age of 64 years.

## DISCUSSION

We determined the comorbidities at baseline in two multicentre French cohorts of ERA (ESPOIR) and ES<sub>Pa</sub> (DESIR), investigating whether they are present in the very early stages of the diseases. Moreover, we compared the prevalence to the French general population.

We found that comorbidities were frequent in patients with ERA and ES<sub>Pa</sub> at baseline, with AHT and dyslipidaemia having the highest proportions. Our results are in line with a previous ERA study, which reported that 43% of 183 patients had at least one comorbid condition at baseline, with a frequency of 12% of AHT.<sup>32</sup> In a cohort of 4794 newly diagnosed patients with AS in Taiwan, Huang *et al*<sup>33</sup> described a frequency of AHT of 2.2% and dyslipidaemia of 2.6%. Interestingly, we found fewer cases of CHD or stroke in ESPOIR patients compared with other studies, and none in DESIR patients. This is in contrast with an excess risk of cerebrovascular

**Table 3** Prevalence (or CI 95%) of TB in patients with ERA (ESPOIR) and ES<sub>Pa</sub> (DESIR) compared with the French general population in 2008

Gender	Age groups	French general population		ESPOIR Patients with ERA		DESIR Patients with ES <sub>Pa</sub>	
		N	Prevalence (%)	N	CI 95% (%)	N	CI 95% (%)
Men	20–39	1276	0.02	0	0 to 12.98	2	0.15 to 3.44
	40–44	430	0.02	0	0 to 26.76	0	0 to 17.81
	45–49	427	0.02	1	0.04 to 37.91	1	0.16 to 17.51
	50–54	427	0.02	0	0 to 12.64	–	–
	55–59	470	0.03	2	1.29 to 25.76	–	–
	60–64	429	0.03	2	1.46 to 28.47	–	–
	65–69	307	0.03	0	0 to 25.35	–	–
Women	20–39	1161	0.02	1	0.02 to 2.77	1	0.02 to 2.70
	40–44	314	0.02	1	0.09 to 9.98	1	0.11 to 12.47
	45–49	319	0.02	3	1.04 to 12.03	1	0.13 to 15.07
	50–54	353	0.02	3	0.92 to 10.69	–	–
	55–59	348	0.02	9	5.2 to 19.41	–	–
	60–64	286	0.02	5	3.16 to 19.41	–	–
	65–69	263	0.02	5	6.53 to 36.48	–	–
Total		6810	0.02	32	4.69 (3.28 to 6.63)	6	0.99 (0.4 to 2.25)

N, number with a diagnosis of tuberculosis in each gender and age group.

DESIR, Devenir des Spondylarthropathies Indifférenciées Récentes; ERA, early rheumatoid arthritis; ES<sub>Pa</sub>, early axial spondyloarthritis; ESPOIR, Etude et Suivi des Polyarthrites Indifférenciées Récentes; TB, tuberculosis.

**Table 4** Comparison of values of traditional CV risk factors stratified by gender in patients with ERA (ESPOIR) and ESaA (DESIR)

	ESPOIR Patients with ERA					DESIR Patients with ESaA				
	Men		Women		p* Value	Men		Women		p* Value
	N	Mean±SD	N	Mean±SD		N	Mean±SD	N	Mean±SD	
Smoking†	149	36 (24.2)	475	95 (20)	0.329	174	67 (38.5)	219	69 (31.5)	0.179
SBP	159	132.3±16.9	518	127.4±15.3	0.001	295	123.5±13.6	332	116.3±13.4	<0.001
BMI	160	25.9±4.1	527	24.9±4.6	0.015	299	24.2±5.0	340	23.7±4.4	0.186
Glycaemia	151	97.7±32.6	490	91.8±26.9	0.026	293	88.0±11.2	326	83.8±12.2	<0.001
TChol	152	193.1±41.3	501	204.5±42.0	0.003	287	185.1±45.7	319	197.7±41.6	<0.001
HDL-cholesterol	80	47.8±15.3	273	60.7±17.9	<0.001	263	49.9±14.3	301	61.3±15.5	<0.001
LDL-cholesterol	80	114.3±33.8	272	119.2±37.5	0.299	260	113.6±36.9	299	117.0±38.4	0.288
TG	152	120.6±63.8	505	105.6±60.3	0.008	287	103.9±77.0	319	100.0±80.1	0.552
TChol/HDL	80	4.2±1.3	272	3.6±1.3	<0.001	262	3.9±1.2	300	3.4±0.9	<0.001
TG/HDL	80	2.8±1.9	273	2.1±2.2	0.011	261	2.3±2	300	1.8±1.5	0.001
PP	158	53.4±11.7	518	51.6±11.8	0.094	295	48.7±10.5	332	44.0±10.2	<0.001

All variables are in mg/dL, unless stated otherwise.

\*Independent samples t test.

†N (%).

BMI, body mass index; CV, cardiovascular; DESIR, Devenir des Spondylarthropathies Indifférenciées Récentes; ERA, early rheumatoid arthritis; ESaA, early axial spondyloarthritis; ESPOIR, Etude et Suivi des Polyarthrites Indifférenciées Récentes; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PP, pulse pressure; SBP, systolic blood pressure; TChol, total cholesterol; TG, triglycerides.

disease described especially in younger patients with AS followed up for 10.2 years.<sup>34</sup> It is important to point out that in the study of Szabo, patients had older age at diagnosis (by more than 10 years) and the development of comorbidities is studied after AS diagnosis, whereas in patients with ESaA we studied comorbidities developed before diagnosis. There were other studies with results

similar to ours, including one cross-sectional study in 150 patients with SpA who did not find any cases of cerebrovascular disease.<sup>35</sup>

We found that the prevalence rates of AHT and TB in patients with ERA and, to a lesser extent, in patients with ESaA were much higher than in the general population of similar age and gender. The increased

**Table 5** Description of FRS (2008) and heart age in ERA (ESPOIR) and ESaA (DESIR) men and women

Gender	Age groups	ESPOIR Patients with ERA			DESIR Patients with ESaA		
		N	FRS 2008 mean±SD	Heart age mean±SD	N	FRS 2008 mean±SD	Heart age mean±SD
Men	30–34	3	4.2±1.4	39.7±4.7	54	3.0±1.4	35.4±4.8
	35–39	12	5.0±2.7	41.3±6.8	40	4.1±2.3	39.0±6.6
	40–44	8	7.0±4.5	45.4±10.1	22	7.1±4.2	46.0±8.7
	45–49	3	7.4±1.3	49.0±3.5	30	10.0±5.3	51.8±10.2
	50–54	19	13.4±8.9	56.7±10.0	–	–	–
	55–59	14	20.0±12.9	63.7±10.5	–	–	–
	60–64	6	24.0±11.5	69.5±8.3	–	–	–
Women	65–69	7	25.2±10.1	70.9±8.6	–	–	–
	30–34	22	1.2±0.3	32.8±1.5	58	1.5±1.0	33.9±4.5
	35–39	22	1.8±0.8	36.6±4.2	58	2.3±1.5	38.0±7.1
	40–44	27	3.2±1.7	43.4±7.4	39	2.9±1.7	41.9±7.8
	45–49	36	5.0±2.5	50.6±10.1	32	4.1±1.7	47.6±8.0
	50–54	42	6.7±4.3	55.7±12.7	–	–	–
	55–59	48	9.0±4.9	63.0±12.5	–	–	–
Total	60–64	29	11.3±5.2	70.0±7.8	–	–	–
	65–69	15	15.2±11.3	70.0±11.3	–	–	–
Total		313	8.3±8.0	54.2±15.1	333	3.7±3.4	40.1±8.9

N, number with FRS calculated.

DESIR, Devenir des Spondylarthropathies Indifférenciées Récentes; ERA, early rheumatoid arthritis; ESaA, early axial spondyloarthritis; ESPOIR, Etude et Suivi des Polyarthrites Indifférenciées Récentes; FRS 2008, Framingham Risk Score (2008).

prevalence of AHT is most striking in young patients, especially women. In the general population, the risk of AHT increases after the age of 55 years for men and 65 for women,<sup>36</sup> while in our cohorts, the prevalence of AHT was increased in women after the age of 45 years. With regard to the prevalence of TB, there are few studies performed in anti-TNF $\alpha$  naïve patients with established RA or in patients with AS. We did not find studies that assess active TB history in ERA or ES $\text{P}\alpha$ . Several studies showed a 2-fold to 10-fold increase in the risk of TB among patients with established RA naïve to anti-TNF $\alpha$  drugs, compared with the general population.<sup>9 37</sup> The rates observed in patients with ERA compared with the general population confirm an even higher risk of TB in ERA than in established RA. An increased prevalence of TB compared with the general population was also present in patients with ES $\text{P}\alpha$ , but only in women. As a possible explanation, some authors suggest that there is an aetiological link between TB and arthritis, proving in mouse models that *Mycobacterium tuberculosis* infection promotes arthritis.<sup>38</sup>

We did not find an increased prevalence of malignancies in patients with ERA and ES $\text{P}\alpha$  compared with the general population. One explanation could be that we had no separate general population data for lymphoma, which is known to be increased in established RA more than solid malignancies. Another reason could be that the risk of lymphoma increases in patients with severe RA and persistently high disease activity over time.<sup>39</sup>

Looking into differences in inflammation markers between patients with comorbidities and patients without comorbidities, we did not find sufficient evidence that inflammation is associated with comorbidities, especially CVD, at onset of arthritis. Moreover, comorbidities in these patients should be actively searched and diagnosed early, in order to receive adequate treatment.

When analysing clinical and biological values of traditional CV risk factors, we found high normal BP with overweight in ERA men and dyslipidaemia in women with ERA and with ES $\text{P}\alpha$ . This increase might appear small quantitatively compared with the recommended ESC targets, but current evidence shows that even mild elevations in individual risk factors can greatly influence total CV risk, especially when several risk factors coexist.<sup>26</sup> Finally, we found an intermediate to high 10-year CV risk in patients with ERA older than 55 years without CVD using three effective algorithms (FRS 1998, FRS 2008 and SCORE) that provide complementary information on different aspects of CV risk (CHD risk, general CVD risk and fatal CV risk). Current ESC guidelines for the management of patients with CV risk factors require the measurement of CV risk to determine the objectives for control of the various risk factors and the need for pharmacological intervention, in addition to lifestyle changes.<sup>26 29</sup> In addition, EULAR recommendations highlight the critical importance of adequate disease control in lowering CV risk. However, evidence

suggests that these recommendations are not being practised either consistently or regularly.<sup>40 41</sup> Our results suggest that established RA and ERA should be regarded as a condition at high risk of CVD and that there is need for early CV risk evaluations. One of the limitations of any systems that estimate risk, including the Framingham system, is that when it is applied to middle-aged persons to calculate the absolute risk, this is not high even though their risk factors may be high.<sup>29</sup> As a way of solving this limitation, the heart/vascular age was proposed. A characteristic of our cohorts, particularly DESIR, is the young age of patients at inclusion. We found that the heart age is much higher than the real age of our patients, which translates to a higher relative level of CV risk than the Framingham score. This may be a useful way of expressing more clearly the CV risk to younger patients. It may also help in the decision-making of CV risk management and improve the compliance of patients.

There are several limitations to our study. First, the comorbid diseases recorded in ESPOIR and DESIR are reported by patients at inclusion in the cohorts. A potential recall bias cannot be excluded; however, several studies have confirmed good agreement between self-reported history of chronic disease and medical records.<sup>32 42</sup> Second, there is a trend for decrease in the prevalence of CVD in the French population. Data from DESIR were collected during the same period as the general population data, but the ESPOIR data were gathered prior to that date, which might have an influence when comparing comorbidities.

In conclusion, we found an increased frequency of comorbidities in patients with ERA or ES $\text{P}\alpha$ , with increased prevalence of AHT and TB compared with the general population. In addition, we found an increased 10-year risk in patients with ERA for developing CVD, and increased heart age in patients with both ERA and ES $\text{P}\alpha$ . These results may provide important information to identify patients at risk, to make a diagnosis of comorbidities early on and ultimately early treatment of the risk factors.

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**Acknowledgements** The ESPOIR cohort was supported by an unrestricted grant from Merck Sharp and Dohme (MSD) allocated for the first 5 years. Two additional grants from INSERM were obtained to support part of the biological database. The French Society of Rheumatology, Abbvie and Pfizer also supported the ESPOIR cohort study. The authors wish to thank Nathalie Rincheval, who did expert monitoring and data management, and all investigators who recruited and followed the patients (FB, Paris-Saint Antoine; MC Boissier, Paris-Bobigny; A Cantagrel, Toulouse; H Cholvy, Montpellier; MD, Paris-Cochin; P Fardelone and P Boumier, Amiens; B Fautrel, Paris-La Pitié; RM Flipo, Lille; Ph Goupille, Tours; F Liote, Paris-Lariboisière; Le Loet and O Vittecoq, Rouen; XM, Paris Bicêtre; O Meyer, Paris Bichat; A Sarau, Brest; Th Schaevebeke, Bordeaux; J Sibilia, Strasbourg). The DESIR cohort is conducted under the control of Assistance Publique-Hopitaux de Paris via the Clinical Research Unit Paris-Centre and under the umbrella of the French Society of Rheumatology and INSERM (Institut National de la Santé et de la Recherche Médicale). The database management is performed within the department of epidemiology and biostatistics (Professor Jean-Pierre Daurès, DIM, Nîmes, France). An unrestricted grant from Pfizer Pharmaceuticals was allocated for the first 5 years of the follow-up of the recruited patients. They also wish to thank the different regional participating centres: Professor Maxime Dougados (Paris—Cochin B), Professor André Kahan (Paris—Cochin A), Professor Olivier Meyer (Paris—Bichat), Professor Pierre Bourgeois (Paris—La Pitié-Salpêtrière), Professor Francis Berenbaum (Paris—Saint Antoine), Professor Pascal Claudepierre (Créteil), Professor Maxime Breban (Boulogne Billancourt), Dr Bernadette Saint-Marcoux (Aulnay-sous-Bois), Professor Philippe Goupille (Tours), Professor Jean-François Maillefert (Dijon), Dr Xavier Puéchal (Le Mans), Professor Daniel Wendling (Besançon), Professor Bernard Combe (Montpellier), Professor Liana Euler-Ziegler (Nice), Professor Philippe Orcel (Paris—Lariboisière), Professor Pierre Lafforgue (Marseille), Dr Patrick Boumier (Amiens), Professor Jean-Michel Ristori (Clermont-Ferrand), Dr Nadia Mehzen (Bordeaux), Professor Damien Loeuille (Nancy), Professor René-Marc Flipo (Lille), Professor Alain Sarau (Brest), Professor Corinne Miceli (Le Kremlin Bicêtre), Professor Alain Cantagrel (Toulouse), Professor Olivier Vittecoq (Rouen).

**Contributors** AMG, MD, BC, RL, CM and DvdH designed the study. MD, BC, FB and XM acquired the data. AMG and RW analysed the data. MD, BC and DvdH oversaw the analysis. AMG prepared the first version of the manuscript and all authors critically revised the manuscript. All authors gave their approval of the final version of the manuscript.

**Funding** AMG was supported by a EULAR scientific training bursary for 6 months.

**Competing interests** None declared.

**Patient consent** Obtained.

**Ethics approval** The ESPOIR study was conducted with the approval of the Institutional Review Board of Montpellier University Hospital, the coordinating centre, and was conducted in accordance with the Declaration of Helsinki and the guidance for good clinical practice (French version), 30 November 2006. All patients gave their signed informed consent to participate in the cohort. The DESIR study was approved by the French Departmental Directorate of Health and Social Affairs (Directeur Départemental des Affaires Sanitaires et Sociales), has obtained the approval of the appropriate local ethics committees and was conducted in accordance with the Declaration of Helsinki and the guidance for good clinical practice (French version), 30 November 2006. All patients gave their signed informed consent to participate in the cohort.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** No additional data are available.

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