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Risk of cardiovascular comorbidities before and after the onset of rheumatic diseases

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ABSTRACT

Objectives: To elucidate the risk and temporal relationship of cardiovascular (CV) comorbidities in rheumatic diseases.
Methods: Patients in the FinnGen study diagnosed between 2000 and 2014 with seropositive (n = 2368) or seronegative (n = 916) rheumatoid arthritis (RA), ankylosing spondylitis (AS, n = 715), psoriatic arthritis (PsA, n = 923), systemic lupus erythematosus (SLE, n = 190), primary Sjogren's syndrome (pSS, n = 412) or gout (n = 2034) were identified from healthcare registries. Each patient was matched based on age, sex, and birth region with twenty controls without any rheumatic conditions. Overall risk ratios (RR) were calculated by comparing the prevalence of seven CV diseases between patients and controls. Logistic regression models were used for estimating odds ratios (OR) for CV comorbidities before and after the onset of rheumatic diseases.
Results: The RR for 'any CVD' varied from 1.14 (95 % confidence interval [CI] 1.02–1.26) in PsA to 2.05 (95 % CI 1.67–2.52) in SLE. Patients with SLE or gout demonstrated over two-fold risks for several CV comorbidities. Among CV comorbidities, venous thromboembolism (VTE) showed the highest effect sizes in several rheumatic diseases. The ORs for CV comorbidities were highest within one year before and/or after the onset of the rheumatic disease. However, in gout the excess risk of CV disease was especially high before gout diagnosis.
Conclusions: The risk of CV comorbidities was elevated in all studied rheumatic diseases, with highest risks observed in SLE and gout. The risk for CV diseases was highest immediately before and/or after rheumatic disease diagnosis, highlighting the increased risk for CV comorbidities across all rheumatic diseases very early on the disease course.

Introduction

Cardiovascular (CV) diseases are the most frequent comorbidities in rheumatic diseases, leading to increased mortality [1–4]. Increased risk for CV diseases is well recognized in rheumatoid arthritis (RA) and gout, but has also been observed in other rheumatic conditions such as systemic lupus erythematosus (SLE), other connective tissue diseases, and spondylarthritis [1,4–27]. Selected traditional CV risk factors may be

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more common among certain rheumatic diseases, but the elevated risk for CV comorbidities is not fully explained by traditional CV risk factors [1,28–30]. In a recent large population-based study, the overall risk of CV diseases among several rheumatic diseases was over 1.5-fold, even after adjusting for traditional risk factors [31].

The elevated CV risk has been shown to be partially connected with increased systemic inflammation accelerating atherosclerosis as well as arterial and venous thrombosis, but studies suggest that the risk for certain CV diseases in RA and SLE is elevated even before the diagnosis [4,32–36]. However, most of the studies provide no information on the temporal relationship between development of CV comorbidity and diagnosis of rheumatic disease. The majority of the studies investigating CV risk in rheumatic diseases have also focused primarily on atherosclerotic diseases and lack information on the risk of other CV diseases such as heart conduction disorders, valvular diseases, chronic heart failure (CHF), and venous thromboembolisms (VTE).

The FinnGen project combines nationwide healthcare registry data with genome data. Using the extensive registry data within FinnGen (N = 321 302), we studied the prevalence and risk of diverse CV comorbidities, and their temporal relationship in seven different rheumatic diseases, comparing the risk to age-, sex- and birth region-matched controls.

Methods

Dataset and rheumatic diseases

FinnGen is a collection of epidemiological cohorts, hospital biobanks, and disease-based cohorts, with their genotypes linked to nationwide health care registries comprising the whole Finnish population. This study uses FinnGen data freeze 7 (N = 321 302). Rheumatic and CV disease cases were identified through the register for specialist health care (HILMO) including both inpatient (from 1969) and outpatient hospital data (from 1998), the national death registry (from 1969), and the social insurance institution of Finland (KELA) registry including data from medication reimbursement (from 1964) and drug purchases (from 1995). The overall quality of HILMO register has been previously evaluated [37], and a recent study demonstrated a positive predictive value of 0.89 for RA diagnosis based on both HILMO diagnosis and KELA medication reimbursement for RA, based on a review of electronic medical records [38]. Follow-up ended at first-ever diagnosis of the CV disease of interest, at death or at the end of follow-up on December 31, 2019, whichever came first.

The study was conducted in accordance with the ethical standards of the institutional and national research committees, with participants providing written informed consent. A detailed ethics statement is presented in Supplementary Data S1.

The rheumatic diseases included in our study were seropositive RA, seronegative RA, ankylosing spondylitis (AS), psoriatic arthritis (PsA), SLE, primary Sjogren's syndrome (pSS) and gout. The rheumatic diseases (except gout) were defined as being entitled to a special reimbursement for medicine expenses for inflammatory rheumatic diseases (KELA reimbursement code 202), with an additional requirement of at least two inpatient or outpatient visits with the specific rheumatic disease diagnosis (see Supplementary Table S2 for details). KELA reimbursement is granted for patients that need treatment with a disease modifying anti-rheumatic drug (DMARD), following a rheumatic disease diagnosis by a specialist in rheumatology or internal medicine. Instead of medication reimbursement, gout patients were required to have at least one drug purchase (allopurinol, febuxostat, probenesid and/or benzbromarone), with an additional requirement of at least one inpatient or outpatient visit with gout diagnosis. RA patients were classified as having either seropositive RA or seronegative RA depending which of these diagnoses was used more frequently at rheumatology department visits. All study cohorts were of European ancestry.

The date of the diagnosis of rheumatic or CV diseases was determined by the first occurrence of the diagnosis in the inpatient or outpatient hospital register. Only cases diagnosed at the age of 16 or older, and between 1st of January 2000 and 31st of December 2014, were included in the cohort. This time frame allowed us to focus on patients diagnosed at the era of more effective treatment options (including biologic drugs) and have at least five years follow-up after the rheumatic disease diagnosis.

For each rheumatic disease case, we randomly selected twenty age- (within 3 years), sex- and birth region-matched controls without any rheumatic disease (see Supplementary Table S3 for details).

CV comorbidities

The CV comorbidities of interest included major coronary heart disease event (CHD event), CHF, atrial fibrillation or flutter (AF), valvular heart disease (VHD), VTE, and ischemic stroke. Finally, 'any CVD' included all of the previously listed CV diseases combined. Harmonized endpoints for these diseases, based on inpatient and outpatient hospital registries, procedure codes, the death registry, and the KELA registry, have been expert curated (see Supplementary Table S4 for details).

Statistical analysis

We calculated the risk ratio (RR) for each CV comorbidity in different rheumatic diseases by comparing the overall prevalence of CV comorbidities between patients with rheumatic diseases and controls by the end of follow-up. To study the incidence of CV comorbidities, odds ratios (OR) between cases and controls for CV diseases were calculated by logistic regression, adjusting for age and sex. First, we compared the incidence of different CV comorbidities before and after the onset of each rheumatic diseases throughout the whole follow-up time. For more detailed temporal analyses, we then calculated the ORs for 'any CVD' at 0–1 years, 1–5 years and 5–10 years before and after the onset of the rheumatic disease. Due to FinnGen privacy protection rules, ORs for sample sizes under five could not be determined.

Function 'epitab' (library 'epitools') was used for risk ratio and confidence interval (Wald, normal approximation) calculation in R (version 4.2.1) [39]. Logistic regression analyses were calculated using function 'glm' in R.

Results

Of the 321 302 individuals we identified 2368 cases of seropositive RA, 916 cases of seronegative RA, 715 cases of AS, 923 cases of PsA, 412 cases of pSS, 190 cases of SLE, and 2034 cases of gout. The characteristics of each rheumatic disease cohort are depicted in Table 1. The proportion of females was dominant among pSS (92.0 %), SLE (88.9 %), seronegative RA (72.9 %) and seropositive RA (69.8 %) cohorts, while the proportion of males was dominant among gout (81.1 %) cohort. The median age at the time of diagnosis ranged from 40.4 years (AS) to 65.7 years (gout), and the average duration of follow-up was very similar (11–12 years) in all the rheumatic cohorts except in gout (7.7 years).

The prevalences of conditions predisposing to CV diseases (hypertension, type 2 diabetes and dyslipidemia) in patients with rheumatic disease at the onset of disease and in controls at equivalent age are presented in Supplementary Table S5. In patients with gout, the prevalences of all these conditions were substantially higher compared to controls, as expected. In other rheumatic diseases, the prevalence of hypertension was higher compared to controls, but there were no significant differences in the prevalences of type 2 diabetes and dyslipidemia among patients and controls.

Prevalence of CV comorbidities in rheumatic diseases

The prevalences of the studied CV diseases were higher in all the

Table 1
Study characteristics.

		Seropositive RA	Seronegative RA	AS	PsA	pSS	SLE	Gout
Total	*n*	**2368**	**916**	**715**	**923**	**412**	**190**	**2034**
Female	*n (%)*	**1653** (69.8)	**668** (72.9)	**363** (50.8)	**511** (55.4)	**379** (92.0)	**169** (88.9)	**385** (18.9)
Age at rheumatic disease onset (Y)	*Median (IQR)*	**56.2** (46.7;63.8)	**54.4** (45.1;61.9)	**40.4** (30.8;50.5)	**51.6** (42.0;58.7)	**53.3** (42.7;60.6)	**47.5** (34.5;58.4)	**65.7** (57.6;73.5)
Age at end of follow-up (Y)	*Median (IQR)*	**68.6** (58.8;75.3)	**66.7** (56.7;73.9)	**52.8** (42.7;63.3)	**63.6** (54.2;71.1)	**65.3** (54.8;73.7)	**58.8** (47.2;71.2)	**74.1** (67.7;80.9)
Duration of follow-up after diagnosis (Y)	*Median (IQR)*	**11.6** (8.1;15.3)	**11.8** (8.1;15.4)	**12.0** (8.3;16.0)	**11.3** (7.8;15.2)	**11.9** (8.2;15.9)	**11.8** (8.5;15.8)	**7.7** (5.5;11.0)

RA = Rheumatoid arthritis; AS = Ankylosing spondylitis; PsA = Psoriatic arthritis; pSS = primary Sjogren's syndrome; SLE = Systemic lupus erythematosus.
IQR = Interquartile range; *Y* = Years.

studied rheumatic diseases compared to controls (Table 2). The most common CV comorbidities among patients with rheumatic diseases in general were AF, with prevalence by the end of the follow-up varying from 7.3 % (AS) to 45.1 % (gout), and CHD event with prevalence varying from 7.7 % (AS) to 36.8 % (gout). AF and CHD event were also the most common CV comorbidities within patients with seropositive or seronegative RA, PsA and pSS. Among CV comorbidities, the combined prevalence of atherosclerotic diseases (including CHD Event and stroke) was highest in all studied rheumatic diseases.

Patients with gout had the highest prevalences of all CV comorbidities, AF (45.1 %) and CHF (39.1 %) being the most common comorbidities among gout patients. Among other studied rheumatic diseases, the prevalences of 'any CVD' were similar in RA, SLE and pSS (32.8–35.4 %). Lowest prevalence of 'any CVD' was observed in AS cohort (21.7 %) which is still high compared to control population with the prevalence of 15.3 %

Risk of CV comorbidities in rheumatic diseases

In order to understand the magnitude of the excess risk of CV comorbidities in rheumatic diseases, risk ratios (RR) for CV diseases were calculated. The relative risk for 'any CVD' was elevated in all rheumatic diseases compared to matched controls, with RR varying from 1.14 in PsA to 2.05 in SLE (Fig. 1). Among the CV comorbidities, VTE displayed the largest effect sizes across several rheumatic diseases (seropositive and seronegative RA, PsA and SLE), with RRs varying from 1.45 in AS to 3.48 in SLE.

SLE patients carried the highest risk for 'any CVD' (RR 2.05, 95 % CI 1.67–2.52). In SLE, the risk was particularly high for VTE with RR up to 3.48 (95 % CI 2.21–5.47), but also markedly elevated for CHF, VHD and stroke (more than two-fold compared to the control population). In pSS, the risks for stroke, CHF, VHD and VTE were clearly increased compared to the matched control population (RRs 1.75–1.98). Patients with gout demonstrated over 1.5-fold elevated risk for all CV diseases studied. The highest risk was observed for CHF (RR 3.07, 95 % CI 2.89–3.26), along with at least two-fold risk for both AF (RR 2.04, 95 % CI 1.93–2.14) and VTE (RR 2.45, 95 % CI 2.18–2.76).

In seropositive and seronegative RA, the risks for all studied CV comorbidities besides stroke were increased, with highest risks observed for CHF (RRs 1.49, 95 % CI 1.30–1.70 and 1.42, 95 % CI 1.11–1.81, respectively) and VTE (RRs 1.58, 95 % CI 1.36–1.85 and 1.90, 1.50–2.39). Among patients with AS, the relative risk for 'any CVD' was 1.41 (95 % CI 1.22–1.63), and the risks for CHD event, VHD, VTE and stroke were increased compared to controls (RRs varying from 1.45 to 1.51). The lowest relative risk for 'any CVD' was observed in PsA (RR 1.14, 95 % CI 1.02–1.26), but especially the risk for VTE was increased compared to matched controls (RR 1.92, 95 % CI 1.51–2.45).

Temporal patterns of CV risk

To evaluate the temporal patterns between rheumatic diseases and CV comorbidities, we calculated odds ratios (ORs) for CV diseases before and after the onset of the rheumatic disease. Overall, the ORs for developing a CV comorbidity were rather similar after the onset of rheumatic disease when compared with the period before rheumatic disease diagnosis (Fig. 2). However, in gout patients the excess risk for CV diseases was markedly higher before gout diagnosis in all the CV comorbidities except stroke, for which the OR was similar before and after the diagnosis. This difference in ORs before and after the diagnosis was especially striking for CHF (OR 7.80, 95 % CI 6.95–8.76 vs. OR 1.37,

Table 2
Prevalence of cardiovascular (CV) comorbidities in rheumatic diseases by the end of follow-up. The number of patients (percentages) with CV diseases are presented.

	Seropositive RA		**Seronegative RA**		**AS**		**PsA**		**pSS**		**SLE**		**Gout**	
	Case	*Control*	*Case*	*Control*	*Case*	*Control*	*Case*	*Control*	*Case*	*Control*	*Case*	*Control*	*Case*	*Control*
Total	**2368**	**47,360**	**916**	**18,320**	**715**	**14,300**	**923**	**18,460**	**412**	**8240**	**190**	**3800**	**2034**	**40,680**
Any CVD	839 (**35.4**)	13,690 (**28.9**)	316 (**34.5**)	4727 (**25.8**)	155 (**21.7**)	2199 (**15.3**)	254 (**27.5**)	4473 (**24.2**)	135 (**32.8**)	1839 (**22.3**)	66 (**34.7**)	644 (**16.9**)	1499 (**73.7**)	19,639 (**48.2**)
CHD event	336 (**14.2**)	5171 (**10.9**)	114 (**12.4**)	1729 (**9.4**)	55 (**7.7**)	757 (**5.3**)	96 (**10.4**)	1692 (**9.2**)	38 (**9.2**)	540 (**6.6**)	17 (**8.9**)	205 (**5.4**)	749 (**36.8**)	9562 (**23.5**)
CHF	209 (**8.8**)	2814 (**5.9**)	65 (**7.1**)	917 (**5.0**)	22 (**3.1**)	333 (**2.3**)	53 (**5.7**)	771 (**4.2**)	34 (**8.3**)	387 (**4.7**)	13 (**6.8**)	114 (**3.0**)	796 (**39.1**)	5193 (**12.8**)
AF	375 (**15.8**)	5938 (**12.5**)	122 (**13.3**)	1966 (**10.7**)	52 (**7.3**)	815 (**5.7**)	98 (**10.6**)	1798 (**9.7**)	46 (**11.2**)	803 (**9.7**)	22 (**11.6**)	244 (**6.4**)	917 (**45.1**)	9007 (**22.1**)
VHD	169 (**7.1**)	2707 (**5.7**)	65 (**7.1**)	968 (**5.3**)	28 (**3.9**)	377 (**2.6**)	52 (**5.6**)	813 (**4.4**)	35 (**8.5**)	401 (**4.9**)	16 (**8.4**)	141 (**3.7**)	373 (**18.3**)	3761 (**9.2**)
VTE	162 (**6.8**)	2048 (**4.3**)	72 (**7.9**)	760 (**4.1**)	29 (**4.1**)	399 (**2.8**)	66 (**7.2**)	687 (**3.7**)	29 (**7.0**)	328 (**4.0**)	20 (**10,5**)	115 (**3.0**)	275 (**13.5**)	2244 (**5.5**)
Stroke	152 (**6.4**)	2706 (**5.7**)	54 (**5.9**)	860 (**4.7**)	28 (**3.9**)	372 (**2.6**)	44 (**4.8**)	857 (**4.6**)	33 (**8.0**)	334 (**4.1**)	13 (**6.8**)	125 (**3.3**)	347 (**17.1**)	4226 (**10.4**)

RA = Rheumatoid arthritis; AS = Ankylosing spondylitis; PsA = Psoriatic arthritis; pSS = primary Sjogren's syndrome; SLE = Systemic lupus erythematosus.
CVD = Cardiovascular disease; CHD = Coronary heart disease; AF= Atrial fibrillation; CHF = Chronic heart failure; VHD = Valvular heart disease; VTE = venous thromboembolism.

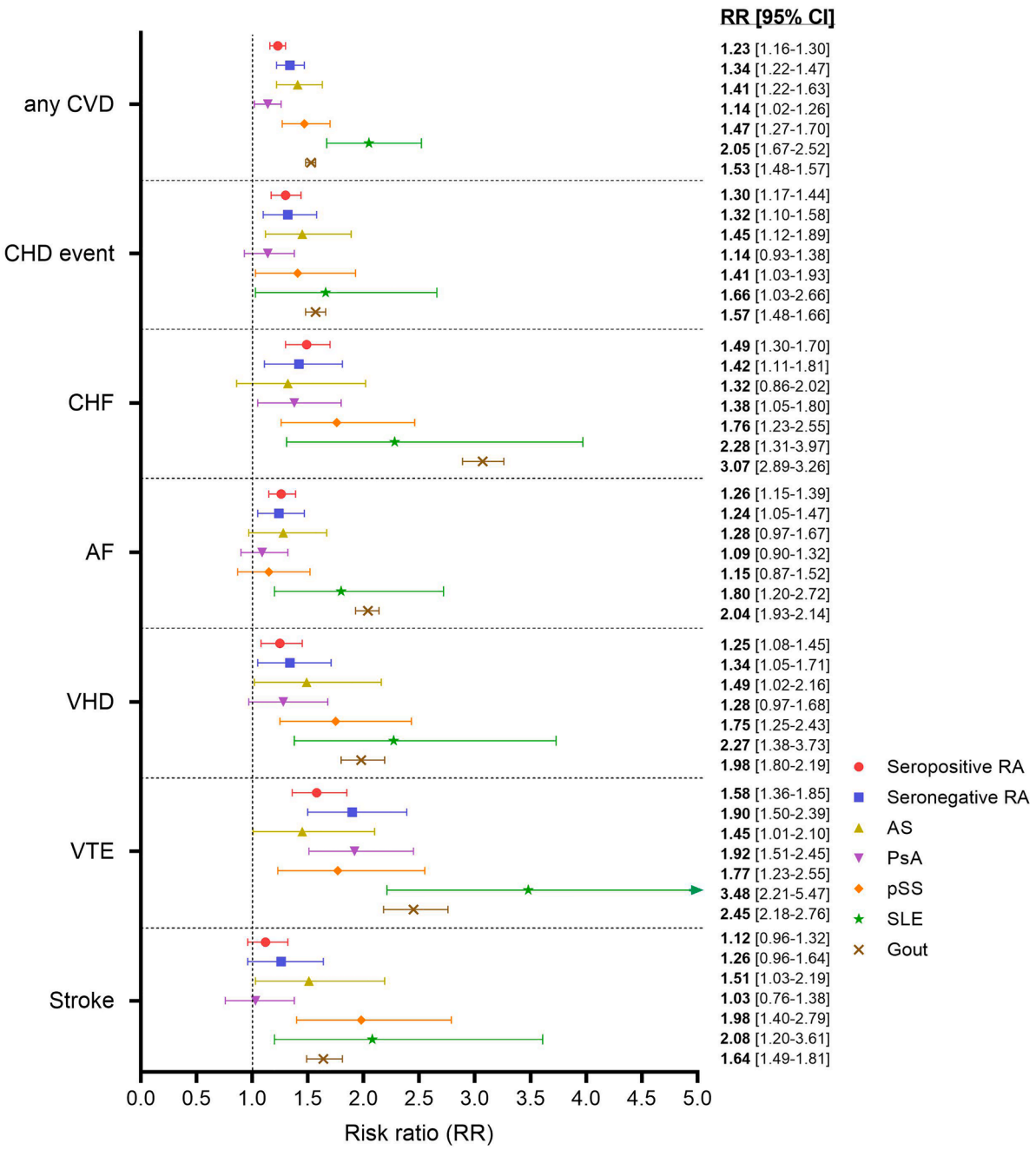

Fig. 1. Risk ratios (RR) and 95 % confidence intervals for prevalent CV comorbidities among rheumatic diseases.
CVD = Cardiovascular disease, CHD = Coronary heart disease, CHF = Chronic heart failure, AF = Atrial fibrillation, VHD = Valvular heart disease, VTE = Venous thromboembolism, RA = Rheumatoid arthritis, AS = Ankylosing spondylitis, PsA = Psoriatic arthritis, pSS = Primary Sjogren's syndrome, SLE = Systemic lupus erythematosus.

1.18–1.59).

To further investigate the incidence of CV diseases in relation to rheumatic disease diagnosis, we calculated the ORs of 'any CVD' at 0–1 years, 1–5 years and 5–10 years before and after the onset of rheumatic disease (Fig. 3). The ORs for 'any CVD' were highest within one year before and/or after the diagnosis of the rheumatic disease in RA, PsA, pSS and SLE. Concerning AS, the ORs for 'any CVD' were highest within five years before the rheumatic disease diagnosis. In gout, the ORs for 'any CVD' were clearly elevated up to ten years before gout diagnosis and within one year after the gout diagnosis, after which the excess risk for 'any CVD' was no longer observed.

Discussion

The risk of CV comorbidities was increased in all the studied rheumatic diseases, with the highest relative risks observed in patients with SLE and gout. Temporal analysis showed that the risk of developing different CV diseases appeared rather similar before and after the onset of rheumatic disease. As an exception, gout patients carried clearly higher relative risk for CV comorbidities before gout diagnosis. Another important finding was that in all of the rheumatic diseases under study, except AS and gout, the excess risk for CV diseases was most evident within one year preceding and/or following the diagnosis of a rheumatic disease.

SLE demonstrated the highest relative risks for most of the CV

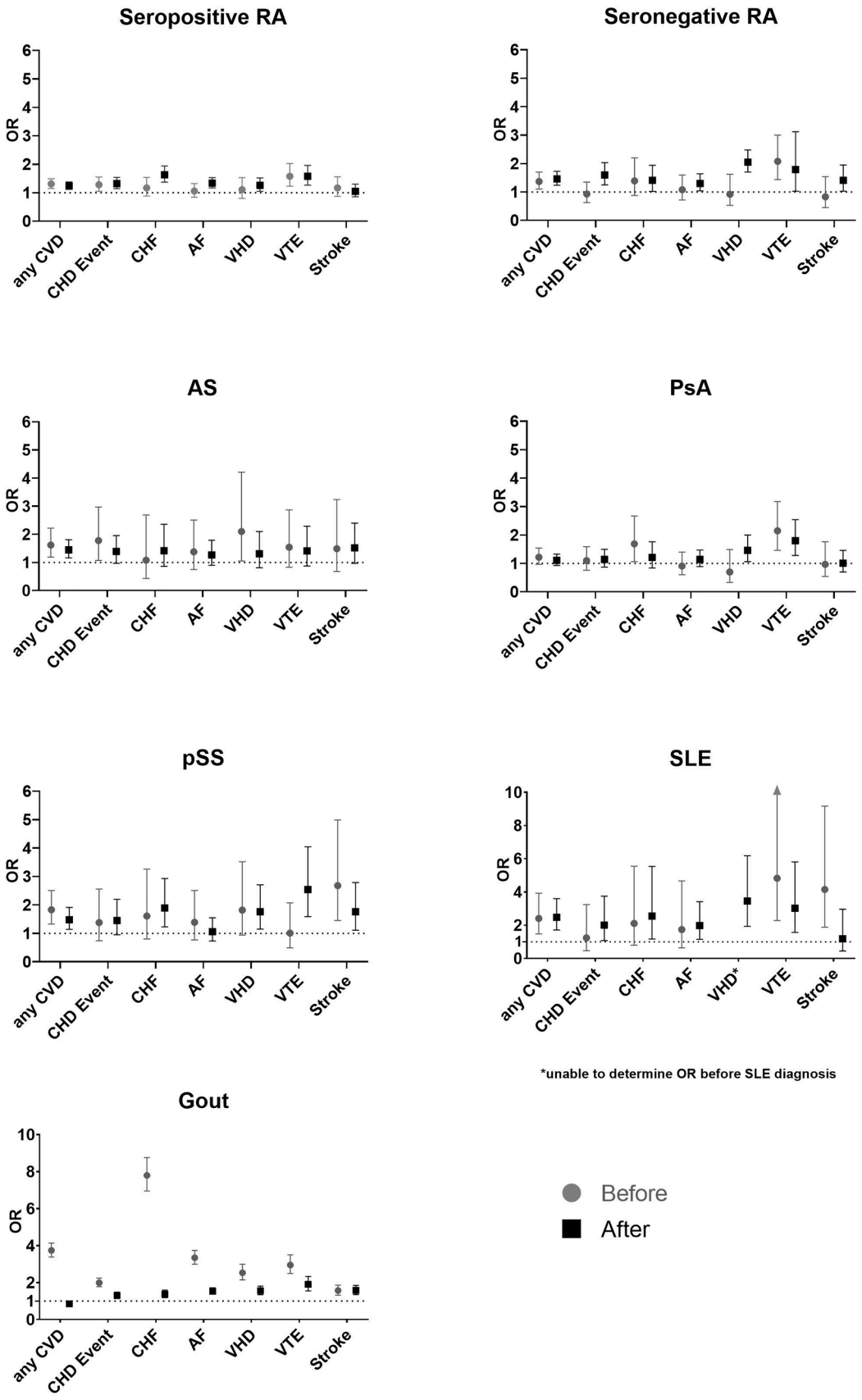

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Fig. 2. Odds ratios (OR) and 95 % confidence intervals of different CV comorbidities before and after rheumatic disease diagnosis. Note the different scales of Y-axis in SLE and gout.
CVD = Cardiovascular disease, CHD = Coronary heart disease, CHF = Chronic heart failure, AF = Atrial fibrillation, VHD = Valvular heart disease, VTE = Venous thromboembolism, RA = Rheumatoid arthritis, AS = Ankylosing spondylitis, PsA = Psoriatic arthritis, pSS = Primary Sjogren's syndrome, SLE = Systemic lupus erythematosus.

comorbidities studied, when compared with other rheumatic diseases. This finding might partly be explained by the young age of SLE patients, resulting into healthier control group. However, our results are also supported by previous studies, even though in our study the relative risk for most of the CV diseases appeared somewhat lower compared to previous findings [4,5,11,31,17–18]. Due to the relative rarity of the disease, the sample sizes in our study and in most of the previous studies were rather small, which might explain variable results. In addition, since our cohort only included SLE patients diagnosed between 2000 and 2014, the somewhat lower risks observed in the current study may result from the fact that SLE patients have received more effective treatment in recent years. Among SLE patients the risk for 'any CVD' was highest within one year before and after SLE diagnosis, and also remained clearly elevated up to 5 years after the diagnosis, suggesting that CV diseases are likely to manifest during clinically active SLE.

Patients with gout also showed markedly elevated risks for all studied CV comorbidities. While this finding is generally in line with previous studies, our results indicate even higher risks for CHF, VTE and AF when compared to previous findings [12–15,19,20]. The majority of gout patients in our study have been treated in special health care and our cohort may thus be enriched with more severe diseases, which might lead to a higher risk profile in our patients compared to gout patients treated in primary health care. An interesting finding in our study was also that, in striking contrast to other rheumatic conditions, gout patients showed clearly higher relative risk for CV comorbidities before and right after the onset of the disease. This might be partially explained by the fact that gout is mainly diagnosed at older age than other studied rheumatic diseases. CV diseases also constitute a significant risk factor for gout[40], and are therefore frequently discovered before or right after gout diagnosis, which may explain the low ORs for 'any CVD' later on after gout diagnosis. In addition, our data demonstrates that hypertension, diabetes and dyslipidemia are substantially more common in patients before the onset of gout compared to controls. Furthermore, the use of diuretics has been shown to act as an important independent risk factor for gout and since they are frequently used in the treatment of CHF, it is reasonable to assume that the OR for CHF was significantly higher before the gout diagnosis than after the diagnosis [41].

The increased risk of CV comorbidities among RA patients has been quite extensively studied, but unlike our study, majority of the previous studies do not differentiate the results between seropositive and seronegative RA. Positive anti-citrullinated protein antibodies (ACPAs) have been associated with pathological carotid intima media thickness and lower left ventricular ejection fraction in RA patients compared to ACPA negative RA patients [42]. However, our current results suggest that the risk for CV comorbidities among seropositive and seronegative RA is in fact similar, which is also in accordance with a recent study from 2020 [43]. In general, the relative risk for different CV comorbidities in RA patients appeared lower in our study as compared to previous results. [5–7,18,21–24] This difference might be partly explained by the fact that many of the previous studies included patients diagnosed before the era of biologic drugs, when the treatment results were poorer compared to patients diagnosed more recently. In addition, since FinnGen data includes largely patients treated in special health care, the prevalences of CV diseases may be slightly higher compared to general population, and this might lead to underestimation of the relative risk of CV diseases in RA and other rheumatic diseases.

The risk of CV diseases among patients with spondylarthritis has been less studied, even though previous studies indicate elevated relative risks for several CV diseases [1,5,8,25–27]. Our results support these findings by showing elevated risks also for less studied CV diseases such as VHD and AF. In our study, the risk for many CV diseases among AS and PsA is consistent with other studies, except for PsA patients showing markedly higher risk for VTE compared to previous findings [9].

Among studied CV comorbidities, the increased risk for VTE was most evident. The elevated risk for VTE is well known in SLE due to the increased prevalence of antiphospholipid antibody syndrome in SLE patients, but not as well recognized among other rheumatic diseases [11]. Limited number of previous studies, however, support our findings, with the exception of PsA and gout expressing even higher relative risk for VTE in our study when compared to previous results [7–11,15, 18]. However, our results also indicate that the prevalence of VTE in rheumatic diseases is still markedly lower compared to major adverse cardiovascular events (MACE; including CHD event and stroke).

Our results support the previous evidence indicating increased risk for CV comorbidities before the diagnosis of RA and SLE, but also further demonstrate similar results concerning other rheumatic diseases including AS, PsA and pSS [4,32–36]. These findings might be explained by the systemic inflammatory activity and serologic abnormalities that have been observed at least in RA and SLE patients even years prior to the onset of symptoms[44,45], as well as by common traditional risk factors (including smoking and hypertension) and genetics for rheumatic and CV diseases. Large genome-wide association studies have discovered numerous genetic risk factors influencing the risk of CV diseases in the population[46,47], but few studies have evaluated their impact in patients with rheumatic diseases[48], warranting further research on the impact of germline genetics of CV diseases in rheumatic diseases. Furthermore, our study indicated markedly elevated risk for CV diseases within one year prior and/or following the rheumatic disease diagnosis. These results could be partly explained by the fact that previously undiagnosed CV diseases are discovered as patients are being followed by doctors after the diagnosis of a rheumatic disease, but may also suggest, as was discussed above regarding SLE, that the increased inflammation due to active rheumatic disease might accelerate the process of developing CV diseases.

Our study has several strengths. This study leverages FinnGen project that allowed identification of rheumatic diseases based on several registries [37,38], and enabled analysis of the temporal relationships of rheumatic and CV diseases. While most of the previous studies have been focused primarily on atherosclerotic diseases, our study adds information on the risk of diverse CV comorbidities in rheumatic diseases. Our study involves only patients diagnosed in the 21st century and therefore provides information on the risk of CV comorbidities in the era of modern treatment, including the era of biologic drugs. In addition, our study offers rarely investigated, but very important, insights to the longitudinal risk of CV comorbidities across rheumatic diseases to gain better insight into the influence of rheumatic diseases to the development of these comorbidities.

Despite the large number of individuals included in FinnGen study, the number of cases especially in the rarer rheumatic disease groups, such as pSS and SLE, remained relatively small, resulting in larger confidence intervals. Due to the same reason, we unfortunately were not able to perform more detailed longitudinal risk analyses for individual CV diseases. In addition, it is important to consider that the temporal risk analyses presented in Fig. 3 do not include individuals diagnosed with CV diseases over 10 years before the onset of rheumatic disease. This exclusion may have an impact on the ORs of 'any CVD' after the onset of the rheumatic disease, as previously discussed in relation to

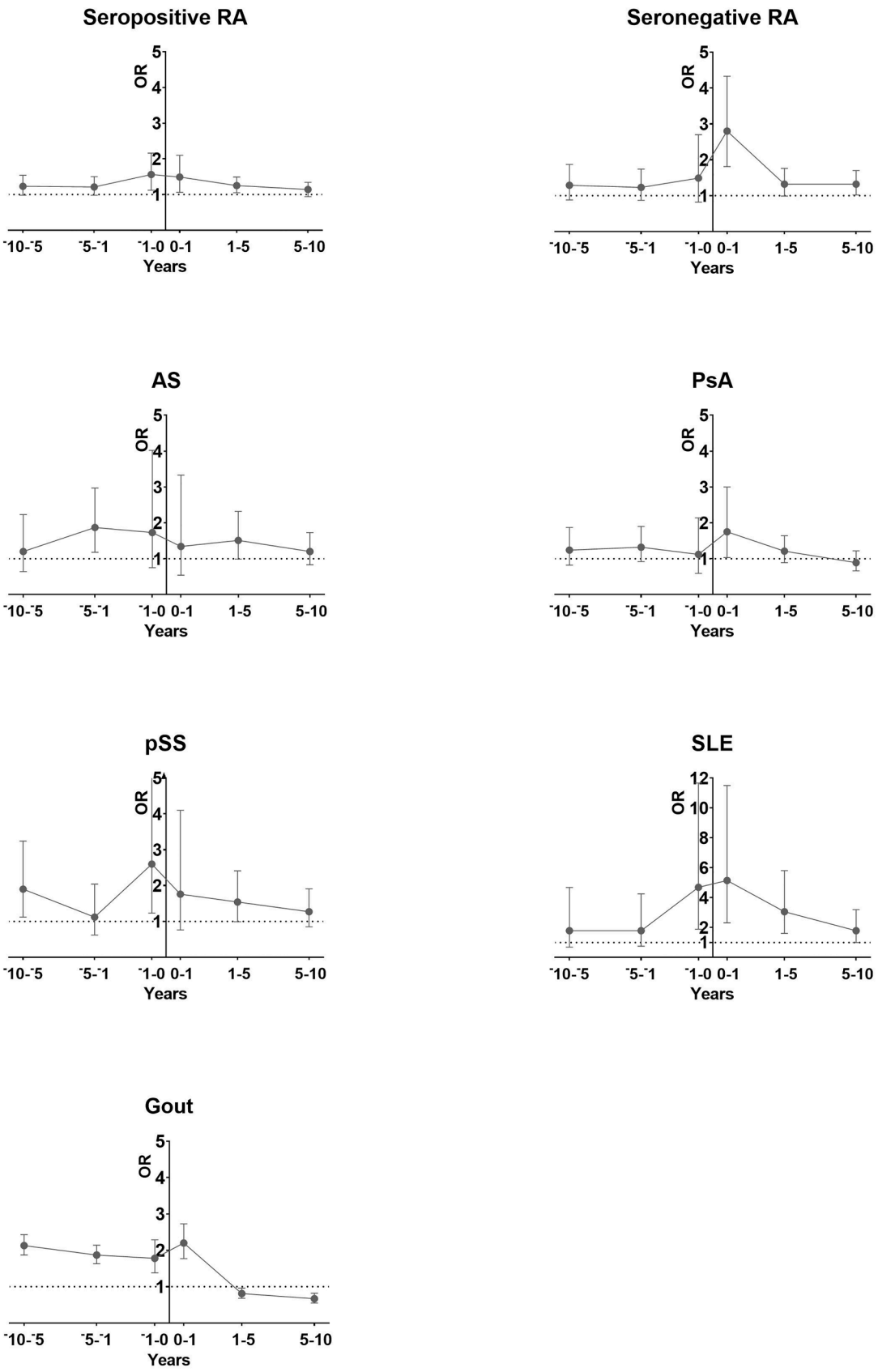

Fig. 3. Odds ratios (OR) and 95 % confidence intervals of 'any CVD' at 0-1 years, 1–5 years and 5–10 years before and after the rheumatic disease diagnosis. Note the different scale of Y-axis in SLE.
CVD = Cardiovascular disease, RA = Rheumatoid arthritis, AS = Ankylosing spondylitis, PsA = Psoriatic arthritis, pSS = Primary Sjogren's syndrome, SLE = Systemic lupus erythematosus.

gout. Lastly, we were unable to account for the impact of traditional CV risk factors, such as smoking or obesity. Future studies are needed to comprehensively assess the impact of these and other CV risk factors, such as hypertension and diabetes, on the temporal relationship of rheumatic diseases and their cardiovascular comorbidities. These evaluations should carefully acknowledge the distinct risk factor and comorbidity profiles of the specific rheumatic diseases.

Taken together, our results emphasize the increased risk for CV comorbidities across all rheumatic diseases very early on the disease course and encourages to consider rheumatic diseases as an independent risk factor for CV diseases. Attention should also be given to the elevated risk for VTE in all patients with a rheumatic condition.

Data availability

Data is available from the authors upon reasonable request.

CRediT authorship contribution statement

Hanna-Kaisa Aaramaa: Conceptualization, Writing – original draft, Writing – review & editing, Visualization, Project administration, Funding acquisition. **Nina Mars:** Conceptualization, Methodology, Formal analysis, Writing – review & editing. **Mika Helminen:** Formal analysis, Writing – review & editing. **Anne M Kerola:** Conceptualization, Writing – review & editing. **Antti Palomäki:** Conceptualization, Writing – review & editing. **Kari K Eklund:** Conceptualization, Writing – review & editing. **Javier Gracia-Tabuenca:** Formal analysis. **Juha Sinisalo:** Writing – review & editing. **FinnGen:** Investigation, Resources, Data curation. **Pia Isomäki:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Hanna-Kaisa Aaramaa: a lecture fee from Novartis and support for attending rheumatological congresses from UCB Pharma and Medac.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2024.152382.

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