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# Discrepancies in risk age and relative risk estimations of cardiovascular disease in patients with inflammatory joint diseases

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ABSTRACT

*Objective:* The European guidelines on cardiovascular disease (CVD) prevention advise use of relative risk and risk age algorithms for estimating CVD risk in patients with low estimated absolute risk. Patients with inflammatory joint diseases (IJD) are associated with increased risk of CVD. We aimed to estimate relative risk and risk age across IJD entities and evaluate the agreement between 'cardiovascular risk age' and 'vascular age models'.
*Methods:* Using cross-sectional data from a nationwide project on CVD risk assessment in IJD, risk age estimations were performed in patients with low/moderate absolute risk of fatal CVD. Risk age was calculated according to the cardiovascular risk age and vascular age model, and risk age estimations were compared using regression analysis and calculating percentage of risk age estimations differing ≥5 years.
*Results:* Relative risk was increased in 53% and 20% had three times or higher risk compared to individuals with optimal CVD risk factor levels. Furthermore, 20–42% had a risk age ≥5 years higher than their actual age, according to the specific risk age model. There were only minor differences between IJD entities regarding relative risk and risk age. Discrepancies ≥5 years in estimated risk age were observed in 14–43% of patients. The largest observed difference in calculated risk age was 24 years.
*Conclusion:* In patients with low estimated absolute risk, estimation of relative CVD risk and risk age may identify additional patients at need of intensive CVD preventive efforts. However, there is a substantial discrepancy between the risk age models.

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## 1. Introduction

Patients with inflammatory joint diseases (IJD), including rheumatoid arthritis (RA), axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA) have increased risk of cardiovascular disease (CVD) compared to the general population [1–3]. Conventional cardiovascular disease (CVD) risk factors (CVD-RFs) have been shown to be prevalent in IJD populations [4–8], thus efficient and accurate CVD risk assessment may be particularly important in IJD [9]. Several CVD risk algorithms have been developed [10] and the Systematic Coronary Risk Evaluation (SCORE) algorithm has been validated for estimation of absolute 10-year risk of fatal CVD in the general, European population [11,12]. Unfortunately, SCORE and other CVD risk algorithms developed for the general population have been proven to inaccurately predict the risk of CVD in patients with RA [13–17] and validated CVD risk models specifically targeted at IJD patients are currently missing. Awaiting the development of more precise CVD risk algorithms for RA patients, the European League against Rheumatism (EULAR) advocate modifying the SCORE (mSCORE) algorithm. This was based on reported standardised mortality ratios and consensus agreement, and the EULAR recommendations advocate applying a 1.5 multiplication factor to the estimated risk of future CVD in patients with RA [18,19].

The latest European guidelines on CVD prevention recommends estimation of 10-year absolute risk of a fatal atherosclerotic event using

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the SCORE algorithm to guide treatment decisions regarding initiation of CVD preventive medication [20]. Furthermore, it is stated in the guidelines that in younger individuals "use of the relative risk chart or calculation of their 'risk age' may help in advising them of the need for intensive preventive efforts" [20], and there are indications that the concept of risk age improves risk communication [21]. The relative risk chart is presented in the ESC 2016 guidelines which also refers to two different risk age algorithms; the 'vascular age' and the 'cardiovascular risk age' model [22,23]. While relative risk is a ratio of the absolute risk of CVD in an individual to the CVD risk given optimal CVD-RF levels with same age and sex, the risk age concept denotes a specific age associated with equal absolute risk given ideal CVD-RFs with the same sex. We questioned whether relative risk and risk age estimation could identify individuals at increased CVD risk among IJD patients who represents a high-CVD-risk population in which validated risk calculators are still missing.

Thus, the aims of this study were to estimate relative risk of CVD as well as cardiovascular risk age and vascular age compared to chronologic age in IJD patients. Furthermore, we aimed to evaluate the level of agreement and/or discrepancies between CVD risk estimations according to the different risk age algorithms. In addition, we evaluated if rheumatic disease related variables were associated with estimated relative risk and the difference between risk age and chronologic age.

## 2. Patients and methods

Patients were recruited from the NOrwegian Collaboration on Atherosclerosis in patients with Rheumatic joint diseases (NOCAR) project [24]. Being a quality assurance project, informed consent was not collected and NOCAR was not submitted for approval by ethics boards since this was not required neither by Norwegian law nor the institution policy. However, the project received the appropriate approvals by Data Protection Officers (ref 2014/11741).

RA/axSpA/PsA patient were included in the current analyses if they had a low-moderate absolute risk, corresponding to a 10-year risk of a fatal CVD events <5% as estimated by applying the SCORE algorithm that includes high-density lipoprotein-cholesterol (HDL-c). For RA patients, the 1.5 multiplication factor was employed. Inclusion was further restricted to patients who were eligible for cardiovascular risk age estimations by being aged 37.5 to 67.5 years. Established atherosclerotic CVD and/or current use of antihypertensive (AntiHT) and/or lipid-lowering therapy (LLT) were exclusion criteria.

In NOCAR, systematic CVD risk assessments are implemented in the follow-up of IJD patients who are attending rheumatology outpatient clinics across Norway. So far, data have been recorded in seven clinics (Oslo [Diakonhjemmet Hospital], Lillehammer [Hospital for Rheumatic Diseases], Kristiansand [Hospital of Southern Norway], Skien [Betanien Hospital], Bergen [Haukeland University Hospital], Drammen (Vestre Viken Hospital) and Tromsø [University Hospital of Northern Norway]).

Data on self-reported CVD comorbidities, history of diabetes mellitus, and use of AntiHT and/or LLT were recorded, lipids (total cholesterol [TC] and HDL-c) were added to routine laboratory tests, and blood pressure (BP) was measured as part of the clinical examination. In case of initial elevated systolic (sBP) or diastolic BP (>140/90 mm Hg), three BP measurements were performed and the average of the last two were recorded.

In addition to CVD related variables, data also included demographic (sex and age), socioeconomic (work status and number of years of education) and rheumatic disease related variables. The latter included specific IJD diagnosis, onset of rheumatic symptoms, serologic markers (rheumatoid factor [RF], anti-citrullinated peptide antibodies [ACPA] and human leukocyte antigen B27 [HLAB27]), markers of inflammation (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]), and composite disease activity scores (Disease Activity Score in 28 joints [25] using ESR [DAS28] and Ankylosing Spondylitis Disease Activity Score [26] using CRP [ASDAS]). Lastly, status of anti-rheumatic treatment (glucocorticoids, synthetic and biologic disease-modifying anti-rheumatic drugs [sDMARDs and bDMARDs]) was also recorded.

Relative risk was calculated according to the relative risk chart published in the ESC guidelines [20]. In detail, relative risk is estimated separately for daily smokers and non-smokers, by finding the nearest corresponding pre-defined sBP levels (120/140/160/180 mm Hg) and TC levels (4/5/6/7/8 mmol/L) in which specific combinations of these risk factors, yield 40 unique risk cells corresponding to particular relative risks ranging from 1 to 12 [20]. Consequently, patients can have one to twelve times the estimated risk compared to an individual of the same age and sex but with optimal CVD-RF levels (non-smoking, sBP of 120 mm Hg and TC of 4 mmol/L). No classification of relative risk levels have previously been defined, thus we defined patients as having no (relative risk = 1), moderately (relative risk = 2) or highly increased relative risk (≥3), respectively.

Similarly, cardiovascular risk age was calculated for males and females by finding the combination of nearest pre-defined age (40/45/50/55/60/65 years), smoking habits (daily smoker/non-smoker), sBP (120/140/160/180 mm Hg) and TC (4/5/6/7/8 mmol/L) levels [23]. For instance, a non-smoking individual with a sBP of 120 mm Hg and TC of 4 mmol/L will have a risk age equal to his/her chronologic age truncated to the nearest 5 year increment.

In the development of the vascular age table Cuende et al. imputed TC at 5 mmol/L, sBP of 120 mm Hg and non-smoking in the SCORE algorithm to derive a reference table of absolute risk in individuals classified as having non-elevated CVD risk factors, for each age from 40 and up to 65 years [22]. Consequently, by calculating the absolute risk, a patient's vascular age may be estimated. In the following analyses, 10-year risk of fatal CVD events was calculated according to four different methods: 1) the former SCORE algorithm without HDL-c (SCORE), 2) the latest SCORE algorithm with HDL-c (SCORE-HDL-c), 3) the mSCORE without HDL-c (mSCORE) and 4) mSCORE with HDL-c (mSCORE-HDL-c). For each of these risk calculations, the estimated absolute risk was compared to the vascular age table [22], to find the estimated vascular age. For non-RA individuals, risk age as calculated using the SCORE algorithm without HDL-c would equal chronologic age if they were non-smokers, had sBP of 120 mm Hg and 5 mmol/L of TC.

### 2.1. Statistics

Nominal data are presented as numbers and percentages. Continuous variables are presented as mean with standard deviation (SD) for normally distributed data, and as median with inter-quartile range (IQR) for non-normally distributed data.

Group differences were evaluated using Chi-square test for dichotomous endpoints. In cases of low cell counts, Fisher's exact test was applied. For continuous dependent variables, one-way analysis of variance (ANOVA) was conducted, whereas Welch ANOVA was used if homogeneity of variance was violated. Furthermore, Kruskal-Wallis tests were used for continuous variables with non-normal distributions.

The difference in years between estimated risk age and chronologic age was calculated for each individual according to the cardiovascular risk age model and the four different vascular age models. For cardiovascular risk age estimations, gap years was calculated by subtracting the nearest corresponding pre-defined age level (40/45/50/55/60/65 years) from the estimated cardiovascular risk age. Since no limits have been previously defined, risk ages ≥5 and ≥10 years above the patient's chronologic age was arbitrarily predefined as moderately and highly elevated risk age, respectively. In a similar fashion, a discrepancy of ≥5 years in risk age estimations between the risk age models was chosen as a substantial level of difference.

Level of agreement between risk age models was investigated using linear regression calculating R square ($R^2$). Percentage of observations in which the risk age models displayed minor (<5 years) and major (≥5 years) discrepancies was calculated. Lastly, median difference between estimated risk age and chronologic age was calculated for different levels of estimated relative risk.

Association between rheumatic disease and antirheumatic treatment related variables to estimated relative risk and difference between risk age was investigated using linear regression models and Kruskal Wallis H test. Statistical significance was set at $p < 0.05$, and all statistical analyses were performed using STATA version 14.

## 3. Results

In total, 1826 IJD patients (RA: 899; axSpA: 506; PsA: 421) without established CVD and/or current use of AntiHT/LLT had a low/moderate 10-year risk of CVD (mSCORE-HDL-c < 5%). Patient characteristics are presented in Table 1.

Overall, 59% were female (RA: 75%; axSpA: 37%; PsA: 52%) and median (inter-quartile range) age and disease duration was 51 (45, 58) and 8 (4, 16) years, respectively. Fifty-one percent of all IJD patients were current users of bDMARDs. In patients with RA, disease remission (DAS28 < 2.6) was present in 55%, while 39% of axSpA patients had inactive disease (ASDAS < 1.3).

While 46% of the total IJD population had an estimated relative risk of 1 (no increased risk of CVD), 33% had twice that risk and 20% had a CVD risk that was three times or higher than the risk given optimal CVD-RFs (Table 2). The highest relative risk calculated was 8. Distribution of relative risk levels (1–8) was similar across IJD entities.

Difference between risk age and chronologic age, according to 1) cardiovascular risk age estimations and vascular age estimations derived by using the 2) *SCORE*, 3) *SCORE-HDL-c*, 4) *mSCORE* and 5) *mSCORE-HDL-c* algorithms is presented in the supplementary material (Fig. A.1). Depending on the specific risk age model, 19–33% had a risk age ≥ 5 to <10 years above their chronologic age, and 4–18% had a risk age 10 years or higher than their actual age. Among our patients, the largest difference between estimated risk age and chronologic age was 26 years. Using the vascular age estimations, 7–35% of the individuals had an estimated risk age below their chronologic age, depending on which specific model was applied. The most extreme observation in which estimated risk age was less than chronologic age was 13 years.

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