

# Largely accelerated arterial aging in rheumatoid arthritis is associated with inflammatory activity and smoking in the early stage of the disease

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## Research article

**Keywords:** rheumatoid arthritis, coronary calcium score, arterial aging

**Posted Date:** August 31st, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-61732/v1>

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**Version of Record:** A version of this preprint was published at Frontiers in Pharmacology on November 26th, 2020. See the published version at <https://doi.org/10.3389/fphar.2020.601344>.

# Abstract

**Background:** Rheumatoid arthritis (RA) patients have a shorter life expectancy than the general population primarily due to cardiovascular comorbidities.

**Objectives:** To characterize arterial aging in RA.

**Patients and methods:** Coronary calcium scores (CCS) were available from 112 RA patients; out of these patients, follow-up CCS were measured of 54 randomly selected individuals. Control CCS were obtained from the MESA database (includes 6000< participants); arterial age was calculated from CCS.

**Results:** RA patients were significantly older ( $10.45 \pm 18.45$  years,  $p < 0.001$ ) in terms of the arterial age compared to the age, gender and race matched controls. The proportion of RA patients who had zero CCS was significantly less ( $p < 0.01$ ) than in the MESA reference group. Each disease year contributed an extra 0.395 years ( $p < 0.01$ ) on top of the normal aging process. However, the rate of the accelerated aging is not uniform, in the first years of the disease it is apparently faster. Smoking ( $p < 0.05$ ), previous cardiovascular events ( $p < 0.05$ ) and high blood pressure ( $p < 0.05$ ) had additional significant effect on the aging process. In the follow-up study, inflammatory disease activity ( $CRP > 5 \text{ mg/L}$ ,  $p < 0.05$ ) especially in smokers and shorter than 10 years disease duration ( $p = 0.05$ ) had the largest impact.

**Conclusions:** Arterial aging is faster in RA patients compared to control subjects, particularly in the first 10 years of the disease. Inflammation, previous cardiovascular events and smoking are additional contributing factors to the intensified coronary atherosclerosis progression. These data support that optimal control of inflammation is essential to attenuate the cardiovascular risk in RA.

## 1. Introduction

Rheumatoid arthritis (RA) is a heterogeneous autoimmune condition, it affects 0.5-1% of the population and is associated with disability and systemic complications [1–3]. Both genetic and environmental factors have a central role in the pathogenesis of the disease, cigarette smoke is the strongest known environmental factor [4–6]. In RA, ongoing inflammation leads to cartilage destruction, bone erosions and subsequent joint deformities. Although the current treatment strategy, principally the widespread use of biological therapies, improved the outcome of the disease, the mortality rate is still considerably higher among patients with RA than among healthy persons and systemic complications, especially cardiovascular (CV) risk due to RA, represent a significant challenge [7, 8]. Although biologicals have a beneficial effect on the CV risk in RA, TNF and IL6 inhibitors often increase the total cholesterol and triglyceride levels [9–11]. In addition to the traditional cardiovascular risk factors (hypertension, diabetes, smoking, hyperlipidemia, alcohol and physical inactivity), the effect of chronic inflammation on cardiovascular mortality is a rapidly developing field of interest [12]. Elevated CRP level is considered as a cardiovascular risk factor [13, 14]. It is noteworthy, that the risk of acute myocardial infarction (AMI) in RA

is similar to the risk of AMI in diabetes mellitus [15]. Coronary artery disease in RA appears more often in multivessel form [16]. In RA, the inflammation is associated with the presence of high-risk plaques [16, 17]. Coronary calcium score (CCS) is a well-established diagnostic marker showing calcium deposits in coronary arteries. It is known to be influenced by several factors including age, gender, race [18] and smoking [19], high CRP levels (defined as higher than 5 mg/L), cardiovascular disease, high blood pressure and diabetes although the connection between diabetes and CCS is controversial [20, 21]. The CCS assessment is a non-invasive method that has a great value in cardiovascular risk stratification, showing a significant association with the medium- or long-term occurrence of major cardiovascular events [22, 23]. The prevalence of coronary artery calcium (CAC) increases with age, ranging from 5% in a middle-aged cohort to more than 50% in an elderly cohort [24]. A meta-analysis including asymptomatic individuals indicated that those with coronary-artery calcification above the median have an 8.7-fold increased risk of future coronary events [25]. In addition, there are data indicating that progression in CCS is associated with higher risk of myocardial infarction [26, 27] and coronary-artery calcification adds information to the prediction of overall mortality [28]. It has been proposed that CAC can be used to estimate the arterial age in adults. Although the increased cardiovascular risk is widely accepted in RA, the risk factors associated with the chronic autoimmune disease are less clear. The traditional cardiovascular risk scores underestimate the real cardiovascular risk in RA [29–31]. CCS is better in CV risk stratification in RA than combinations of the traditional CV risk factors [32, 33]. Here we investigated the baseline and follow-up CCS of RA patients and studied its progression over time. Our present result underscore the impact of inflammation on the CV risk in RA, especially in the first ten years of the disease.

## 2. Patients And Methods

### 2.1 Patients and controls

All RA patients were recruited in the rheumatology outpatient department of the Semmelweis University (Polyclinic of Hospital Brothers of St. John of God, Budapest, Hungary). Patients ≥ 18 years of age, diagnosed with RA ( $n = 112$ ) according to the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria [34] were enrolled. Exclusion criteria included: concomitant autoimmune disease, except Sjögren's syndrome, malignant diseases, chronic infections with or without fever, known psychiatric disease. The demographic data and the clinical parameters of the patients are summarized in Tables 1 and 2. Hypertension, diabetes mellitus, hyperlipidemia was evaluated based on the standard criteria, smoking history was recorded (smoker/non-smoker). Disease activity was evaluated by using the 28-joint counts and erythrocyte sedimentation rate based (disease activity score/DAS28) score at each visit. Medications were recorded including glucocorticoids, NSAIDs, conventional and targeted disease-modifying antirheumatic drugs (DMARDs) and statins. Both, national and institutional ethics committees approved the study and informed consent was obtained from each individual [*approval number: IF 567-4-2016*]. This work was carried out in accordance with the Helsinki Declaration.

Table 1  
Patient characteristics, categorical variables

| <b>Variable</b>           | <b>No</b> | <b>Yes</b> | <b>Total</b> | <b>Percent%</b> |
|---------------------------|-----------|------------|--------------|-----------------|
| <b>Female</b>             | 18        | 94         | 112          | 83.9            |
| <b>Smoking</b>            | 61        | 49         | 110          | 44.55           |
| <b>DM</b>                 | 95        | 17         | 112          | 15.18           |
| <b>CVevent</b>            | 95        | 17         | 112          | 15.18           |
| <b>HT</b>                 | 42        | 70         | 112          | 62.50           |
| <b>RF positivity</b>      | 36        | 76         | 112          | 83.04           |
| <b>aCCP positivity</b>    | 46        | 66         | 112          | 60.71           |
| <b>high ESR</b>           | 87        | 25         | 112          | 22.32           |
| <b>CRP 5</b>              | 71        | 41         | 112          | 36.61           |
| <b>Biological therapy</b> | 52        | 60         | 112          | 53.57           |

DM: diabetes mellitus (Type I: 3, Type II: 14), HT: hypertension, high ESR for males: ESR > 15 if age is less than 50 and 20 if age is above 50. For females: 20 if age < 50 and 30 above 50. CRP above 5 mg/l.

Table 2  
Patient characteristics, continuous variables

| Variable   | N   | Mean   | SD.    | Min   | Max     |
|------------|-----|--------|--------|-------|---------|
| Age        | 112 | 63.00  | 11.40  | 35.00 | 84.00   |
| Disdur     | 112 | 12.09  | 10.20  | 0.50  | 58.00   |
| CCS        | 112 | 253.25 | 488.30 | 0.00  | 3379.00 |
| HDL        | 109 | 1.64   | 0.42   | 0.82  | 3.66    |
| Chol       | 111 | 5.48   | 1.11   | 3.40  | 8.50    |
| Hba1c      | 110 | 5.67   | 0.75   | 4.40  | 9.40    |
| CRP        | 112 | 7.08   | 12.89  | 0.06  | 79.00   |
| DAS        | 112 | 3.16   | 1.36   | 0.57  | 6.63    |
| Artage     | 112 | 62.22  | 19.86  | 39.10 | 98.01   |
| artAge_dif | 112 | 10.45  | 18.53  | 35.35 | 52.56   |

The arteries are approximately 10 years older in RA compared to the matched control group. Disdur: disease duration, time from diagnosis; CCS: coronary calcium score; Artage: calculated arterial age using Eq. 1, artAge\_dif – arterial age difference from the median of the race, sex and age matched control population

Control population: the Multi-Ethnic Study of Atherosclerosis (MESA) database was used as control. MESA is a prospective cohort study with an aim to investigate predictors of cardiovascular risk factors; coronary artery scan was performed in 6814 participants without apparent cardiovascular problems. We refer to this population as “healthy” population or “MESA” population [35]. Age, gender, and race matched control data were generated by using the online CCS calculator (<https://www.mesa-nhlbi.org/Calcium/input.aspx>). Based on demographic data and the measured CCS, the online calculator provided the estimated probability of having higher than zero calcium, and the 25th, 50th (median), 75th, and 90th CCS percentiles of in a “healthy” (i.e., without apparent cardiovascular disease) population. Using these percentiles and inverse quantile transformation we simulated 100 age, gender and race adjusted CCS for each patient in our study. In this way the control population consisted of 100 age, gender and race matched subjects from the MESA database for each RA patient, altogether 11200 subjects.

## 2.2 Measurement of CCS

All RA participants underwent non-contrast enhanced, prospectively ECG-triggered scan of the heart using a 256-slice multidetector CT (Brilliance iCT 256; Philips Healthcare, Best, The Netherlands) at the Heart and Vascular Center of Semmelweis University. Images were acquired in cranio-caudal direction during a single breath-hold in inspiration, at 78% of the R-R interval, with a slice thickness of 2.0 mm. The following acquisition parameters were used: 128 mm × 0.625 mm detector collimation, 270 ms gantry

rotation time, 120 kV tube voltage, 30 mAs tube current. The quantification of CAC was performed on the axial images on a per-patient and per-vessel basis using a semi-automatic software (Heartbeat-CS, Philips Healthcare, Best, The Netherlands). CCS were computed by the standard calcium scoring algorithm of Agatston [36]. Follow up CCS measurement was performed for 54 patients.

## 2.3 Determination of the arterial age and arterial age difference (artAge\_dif)

Arterial age is an easy to understand intuitive concept, it shows the apparent age of arteries using healthy population as a reference. Therefore, to help the clinical interpretation of the results, CCS were transformed into “arterial age” using the formula of McClelland et al [37]:

$$\text{Arterial Age} = 39.1 + 7.25 \log (\text{CCS} + 1)$$

To facilitate the statistical inference, we introduced an additional variable called artAge\_dif. The variable artAge\_dif measures difference between the observed and the control arterial\_ages. For each patient there were 100 age, gender and race matched controls and we obtained artAge\_dif by subtracting the median of the corresponding controls from each observed value.

## 2.4 Statistical Analysis

Stata version 15 (StataCorp LP, College Station, TX) was used for statistical analysis and R [38] with several additional packages such as ggplot2 [39] for additional programming tasks and visualization. The difference between the measured and MESA control population values were tested using the one-sample alternative of the tests, that is we assumed that simulated control population is not different from the “true” population. Percentages of subjects of having non-zero CCS in the observed and computer predicted populations were compared with exact binomial test. The effect of factors that may influence CCS were studied by graphical analysis followed by univariate testing and multivariate linear regression modeling. Due to highly non-normal distribution of the data we gave preference to nonparametric methods such as rank-based tests or we took the advantage of the “robust” option available for many procedures in Stata. To illuminate the trends, we fitted locally weighted polynomial regression commonly known as LOWESS. Descriptive summaries such as proportion, means, standard deviation (SD) are provided for all clinically relevant baseline variables statistical significance level was set to  $p < 0.05$ , two-tailed.

## 3. Results

### 3.1 Accelerated arterial aging in RA

CCS were measured in 112 RA patients; control CCS were obtained from the MESA database. Figure 1 **upper panel** compares the two arterial age distributions. Both histograms can be split into two parts. There is one single outstanding bar which represents subjects with zero CCS, the arterial age of these subjects is by definition exactly 39.1. A characteristic feature of both curves a rightly skewed distorted bell

shape kind of part ranging from 39.1 up to hundred. These parts correspond to subjects having higher than zero CCS. Although the general features are similar, there are noteworthy differences between the two histograms. Smaller percentage of RA patients have zero CCS and compared to controls, the center of the histogram is shifted to right, towards older ages. These visual impressions were confirmed by the statistical analysis. The CCS calculator gave the probability for each patient having higher than zero calcium. The average of these predicted probabilities was 0.517 while the found ratio is 0.642. The difference between the groups is highly significant ( $p = 0.008$ ).

The assumption that arteries are older in RA compared to the matched controls were further tested with the help of variable artAge\_dif which is the difference of the observed value from the median of the controls. Statistical theory suggests that if there is no difference between the MESA and RA populations then the distribution of artAge\_dif has symmetric distribution around zero. Figure 1 **lower panel** shows that the difference distribution is not symmetric but clearly right skewed with a median of 6.34 years. This difference from the expected zero is highly significant ( $z = 5.51, p < 0.0001$ ). Because artAge\_dif has right skewed distribution (Fig. 1 **lower panel**) the mean difference is higher than the median. As Table 2 shows, the mean difference is 10.45 (SD:18.45) years which means that the arteries of the RA patients in average are 10.45 years older than those of their MESA counterparts' ( $p < 0.001$ ).

## 3.2 Correlation of inflammatory markers with clinical measures

As expected, the inflammatory markers (CRP, ESR) strongly correlated with each-other and with the clinical disease activity (DAS28) **Supplementary Fig. 1**. The correlation between artAge\_dif and the disease duration is also significant ( $r = 0.22, p < 0.05$ ).

## 3.3 Comorbidities, autoantibodies (ACPA/RF), smoking and the arterial age

Figure 2 displays the dependence of artAge\_dif on categorical covariates. The differences between non-smokers/smokers, patients without and with cardiovascular events and patients with normal and high blood pressure were significant ( $p = 0.016, 0.029$  and  $0.023$  respectively). By contrast neither the presence of rheumatoid factor (RF), anti-citrullinated protein antibody (ACPA), nor diabetes proved to be predictive. We also checked if the previous statistical conclusions remain valid if we exclude diabetic patients' data from the analysis. Seventeen patients (15.1%, Table 1) had diabetes. Excluding these individuals, 64.3% of the remaining patients had CCS above zero. This ratio is still significantly higher than the age and gender matched MESA control (49.4%,  $p = 0.004$ ). The same is true for the difference from the matched medians (6.12-year,  $p < 0.001$ ).

## 3.4 The effect of cardiovascular disease on the coronary calcium score

Existing cardiovascular disease or history of cardiovascular events are associated with higher CCS [40]. Subjects with existing cardiovascular condition were excluded from the MESA study while 17 patients in our RA study group (15.18%, Table 1) had pre-existing cardiovascular conditions. Therefore, the question arises to what extent the observed differences are due to the cardiovascular events. To answer this question, we split the RA study group into four subpopulations using criteria that a patient had a zero CCS or the CCS was above it and that a patient had or had not previous cardiovascular disease. In the left panel of **Supplementary Fig. 2** proportions of patients with zero CCS are compared. Both RA subgroups are significantly different from their corresponding matched samples though the difference is much more pronounced in patients with previous cardiovascular disease (**Supplementary Fig. 2**) ( $p = 0.023$  and  $p = 0.005$  respectively). Such difference between the two RA patient subgroups is not seen in the right panel of **Supplementary Fig. 2**, the medians of the matched arterial age differences are practically the same (16.7 years and 18.1 years) for patients without and with cardiovascular disease. Both of them are significantly different from the expected zero ( $p < 0.001$ ). These data suggest, that the effect of RA on the CCS is mostly due to the accelerated progression rate. Cardiovascular disease is an additional risk factor because patients with cardiovascular disease have accelerated conversion rates from being CCS negative to CCS positive. The rate of conversion is significantly higher not only to control ( $p = 0.005$ ) but also compared to RA patients without cardiovascular disease ( $p = 0.012$ ).

### **3.5 Arterial aging is more accelerated in the first 10 years of the disease**

The analysis presented above suggests that the rate of the calcium build-up process in the control and RA populations are markedly different. Indeed, the time from the onset of the disease (disdur) was the only variable which showed significant correlation with the arterial age acceleration (**Supplementary Fig. 1**). However, as the left panel of Fig. 3 shows, the aging process is not constant. It increases monotonically ( $r_s=0.249$ ,  $p = 0.008$ ) but the fitted non-parametric regression line (span = 0.9) suggests that the increase is faster in the first 10 years. Nevertheless, to get a numerical estimate of the arterial aging relative to the control we fitted linear regression between disdur and artAge\_dif. The fitted regression line is displayed in the right panel of Fig. 3. The slope of the regression line is 0.395 (95%CI 0.10–0.68), significantly different from zero ( $t = 2.74$ ,  $p = 0.007$ ) The meaning of this 0.395 is that difference from the control increases by 0.395 year in every year of the disease, thereafter in average every year with RA contributes 0.395 extra arterial years.

### **3.6 Progression rate estimation using follow-up data**

Fifty-four patients had a follow-up CCS measurement, **Supplementary Table 1** summarizes the DAS, CRP and ESR values at the time of the two measurements. Generally, there is strong correlation between these values (**Supplementary Fig. 3**). The average time between the CCS scans was  $1.28 \pm 0.35$  years. The annual arterial aging rate was calculated by dividing the difference between the second and first arterial age measurements with the length of the time interval between the two measurements. The least-square estimates with the corresponding 95% confidence intervals are shown in the left panel of Fig. 4. The

estimated aging rate is 1.44 (95%CI 0.77–2.11) which is in good agreement with the previous regression estimate. Nevertheless, from the further analysis we excluded two subjects who converted during the observation period (i.e., their first CCS was zero and the second above zero, with estimated aging of 8.1 and 12.8 years respectively) because from a statistical viewpoint they were gross outliers. Without these two values the rate estimate was  $1.09 + 0.22$ , still highly different from zero ( $p < 0.001$ ,  $t = 4.78$ ). Additional regression analysis showed that the aging process is significantly faster in patients who had elevated CRP ( $> 5 \text{ mg/L}$ ) level ( $p = 0.024$ ) and in case the time since diagnosis is less than 10 years ( $p = 0.05$ ). The least-square approach allowed us to investigate the combined effect of two or more risk factors, Fig. 4 demonstrates that in smokers with elevated CRP levels the arterial aging rate is doubled. The additionally computed non-parametric test confirmed the significance of the elevated CRP ( $p = 0.0494$ ). The middle and the right panel of Fig. 4 further demonstrates the effect of CRP and disease duration  $< 10$  years on the arterial aging.

### 3.7 Effect of medications on the coronary calcium score

None of the applied treatments influenced significantly the arterial aging progression, based on our CCS measurement follow-up data.

## 4. Discussion

Primarily due to cardiovascular comorbidities patients with RA die significantly earlier [7, 15] the risk of sudden cardiac death is doubled in RA compared to the general population [16, 41–43]. Due to the accelerated cardiovascular risk, the precise risk evaluation is essential. Our present data confirm and extend previous observations regarding the increased cardiovascular risk in RA. Here we show for the first time the profound effect of RA on the arterial age, compared to the MESA population. Older arterial age was associated with smoking, previous cardiovascular events and hypertension. The follow-up substudy was self-controlled and highlighted the importance of other additional factors. Ongoing inflammation (CRP  $> 5 \text{ mg/L}$ ) especially in smokers and shorter disease duration ( $< 10$  years) accelerated arterial aging according to our follow-up data. Therefore, the increased cardiovascular risk due to RA increases with the disease years but the augmentation is not linear, in the first 10 years of the disease the arterial aging is apparently more pronounced.

Inflammation plays a central role in the pathogenesis of atherosclerosis; elevated levels of C-reactive protein (CRP), interleukin-6, and N-terminal pro-hormone B-type natriuretic peptide (NTproBNP) correlate closely with cardiac events [44]. Epidemiological studies suggested that chronic inflammation is associated with higher cardiovascular risk. In addition, inflammation is a recognized risk factor of AMI in RA [45]. A number of inflammatory mediators have been widely studied, both as surrogate biomarkers and as causal agents, in the pathophysiological network of atherogenesis and plaque vulnerability [46]. Low disease activity is associated with a decreased risk of CVE in RA [47] In patients with RA, inflammatory markers, disease severity, and RF positivity, were found to be associated with the risk of

atherosclerosis [48]. ACPA and RF are both unfavorable prognostic factors in RA, in accordance with our present data both autoantibodies are independent from the accelerated arterial aging in RA [49].

The age is an independent risk factor for cardiovascular diseases, nevertheless often the atherosclerotic disease burden is discordant with a patient's chronological age. Calcium is a general component of the atherosclerotic plaque, but not that of the normal vessel wall [23]. Because of this structural difference, the calcium is an accurate index of atherosclerotic disease burden and a useful tool to estimate the risk of cardiovascular adverse outcomes [27, 50]. Previous studies showed the importance of age specific CCS percentiles to predict the occurrence of a cardiovascular event in patients with a similar risk profile [51]. CCS is a widely accepted marker of coronary atherosclerosis. In the MESA population, a doubling of the CCS increased the probability of a coronary event by 25% in a 3.8-year follow-up period. Importantly, this predictive value was relatively stable across different ethnic groups [52]. Similarly to our present data, RA severity was associated with the greater prevalence of coronary artery calcification compared to the MESA population [20]. The Framingham risk score includes age, gender, total and HDL cholesterol, blood pressure, diabetes, and smoking. However long-standing RA had higher Framingham risk scores compared with patients with early disease or control subjects. Furthermore, longstanding inflammation represent additional cardiovascular risk [53]. Moreover, the presence of CAC has been shown in early RA as well [54]. The lack of diabetes effect in our study was somewhat surprising because it is generally presumed that the CCS is independently associated with incident coronary heart disease in diabetes [55]. Framingham risk based on arterial age is more predictive of short-term incident coronary events than Framingham risk based on the observed age [37].

According to recently published data, coronary artery calcification increases with higher total prednisone dose, by contrast methotrexate and other csDMARDs do not influence coronary plaque progression [33]. Furthermore, DMARD and TNF- $\alpha$  antagonists are associated with reduced risk of myocardial infarction, stroke and cardiovascular death [56, 57]. In the present study we did not find any significant effect of the anti-inflammatory or lipid lowering therapies. However, the limited study power prohibits to draw any definite conclusions regarding the effect of statins and targeted therapies on arterial aging. There are other limitations of our work as well: most of our patients had moderate disease activity and untreated patients with early disease were not included in this study.

## 5. Conclusion

- RA significantly accelerates arterial aging; additionally to other risk factors, inflammation might be the pathophysiological link between RA and the increased calcification process. Further larger studies are needed to investigate the potential clinical benefit of CCS measurement in RA patients with risk factors for ischemic coronary heart disease.

## 6. Abbreviations

|      |                                     |
|------|-------------------------------------|
| ACPA | Anti-citrullinated protein antibody |
|------|-------------------------------------|

|          |   |
|----------|---|
| AMI      | Acute myocardial infarction                       |
| CAC      | Coronary artery calcium                           |
| CCS      | Coronary calcium scores                           |
| CI       | Confidence interval                               |
| CRP      | C-Reactive Protein                                |
| CT       | Computed tomography                               |
| CV       | Cardiovascular                                    |
| CVE      | Cardiovascular event                              |
| DAS28    | Disease Activity Score-28                         |
| DMARD    | Disease-modifying antirheumatic drugs             |
| ECG      | Electrocardiography                               |
| ESR      | Erythrocyte sedimentation rate                    |
| HDL      | High-density lipoprotein                          |
| IL-6     | Interleukin-6                                     |
| LOWESS   | Locally weighted scatterplot smoothing            |
| MESA     | Multi-Ethnic Study of Atherosclerosis             |
| NSAID    | Nonsteroidal anti-inflammatory drug               |
| NTproBNP | N-terminal pro-hormone B-type natriuretic peptide |
| RA       | Rheumatoid arthritis                              |
| RF       | Rheumatoid factor                                 |
| TNF      | Tumor necrosis factor                             |

## 7. Declarations

### 7.1 Ethics approval and consent to participate

Both, national and institutional ethics committees approved the study and informed consent was obtained from each individual [approval number: IF 567-4-2016]. This work was carried out in accordance with the Helsinki Declaration.

## 7.2 Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

## 7.3 Competing interests

NM, ZT, LT, AB, AIN, AS, DB, PMH, BM, GN have declared no conflicts of interest.

## 7.5 Funding sources

This publication was supported by the National Research, Development and Innovation Office of Hungary (NVKP\_16-1-2016-0017 National Heart Program) and by Hungarian Scientific Research Fund Grant K 131479. The authors are grateful for the investigators, the staff, and the participants of the MESA study. Al Nagy was supported by the János Bolyai Scholarship of the Hungarian Academy of Sciences.

## 7.4 Authors' Contributions

NM: Design of the study, data collection, first draft of the manuscript, data interpretation

## 7.6 Acknowledgements

We are grateful for the outstanding work of Zsófia Tarcza ultrasound technician.

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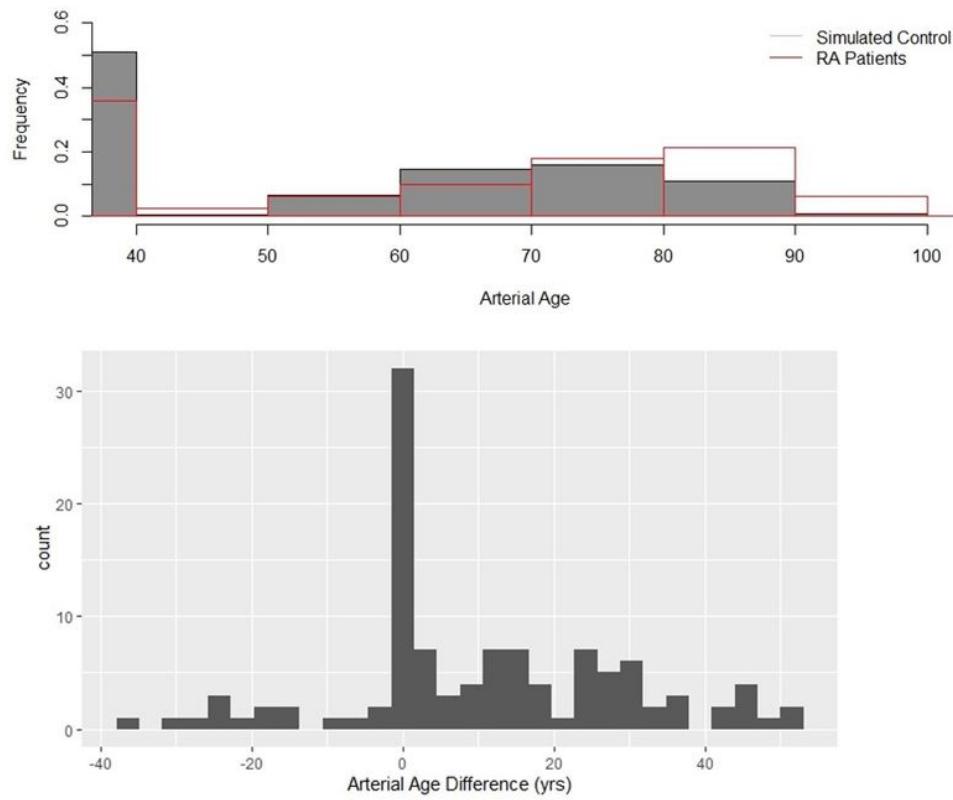
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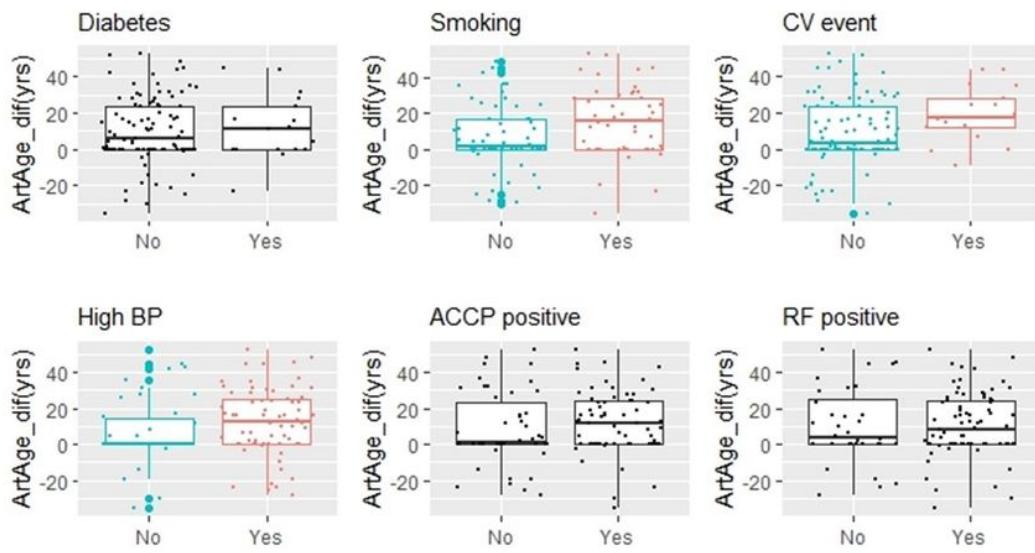
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## Figures



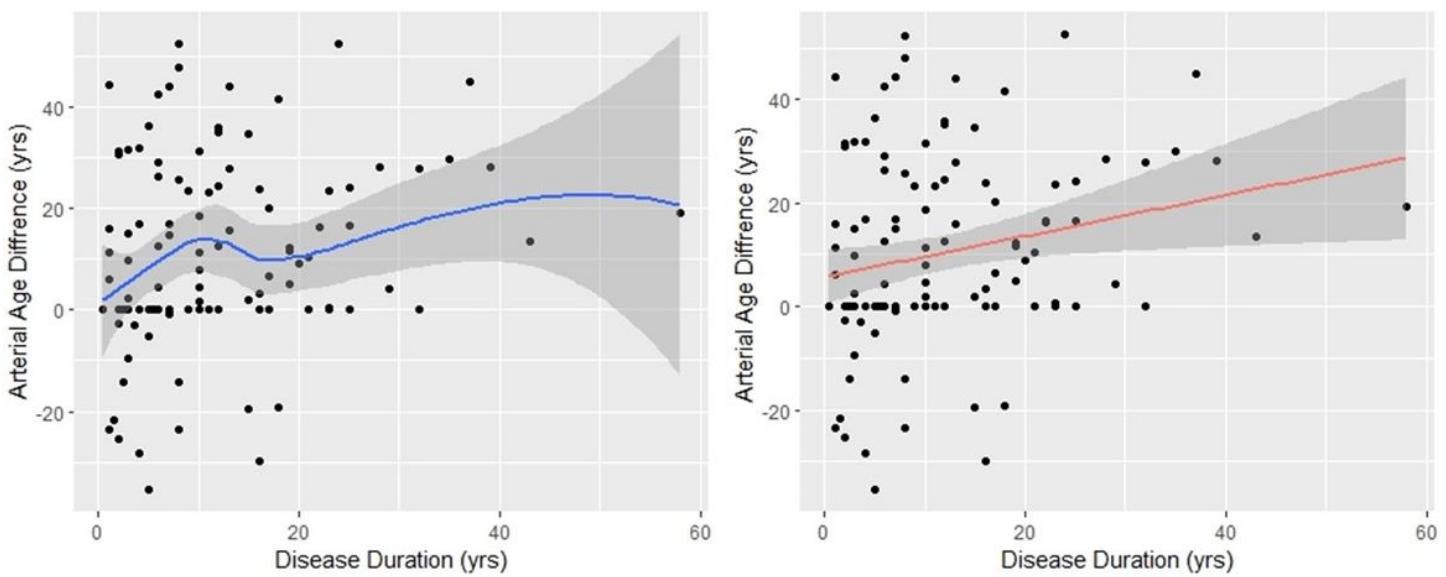
**Figure 1**

Arterial age in rheumatoid arthritis Upper panel: Arterial age, converted from the observed and age, gender and race adjusted simulated coronary calcium scores. The figure shows the resulting distributions of the observed and simulated data. The shaded bars are the simulated control subjects, the transparent bars with red contours represent the observed values. Lower panel: The arterial age distributions of patients with RA and the control populations are different. ArtAge\_dif is the difference between the observed and the median of the control arterial ages. If there is no difference between RA patients and control subjects then the histogram of artAge\_dif must be symmetric around zero. Using Wilcoxon signed test we showed that this null hypothesis is unlikely ( $p<0.001$ ).



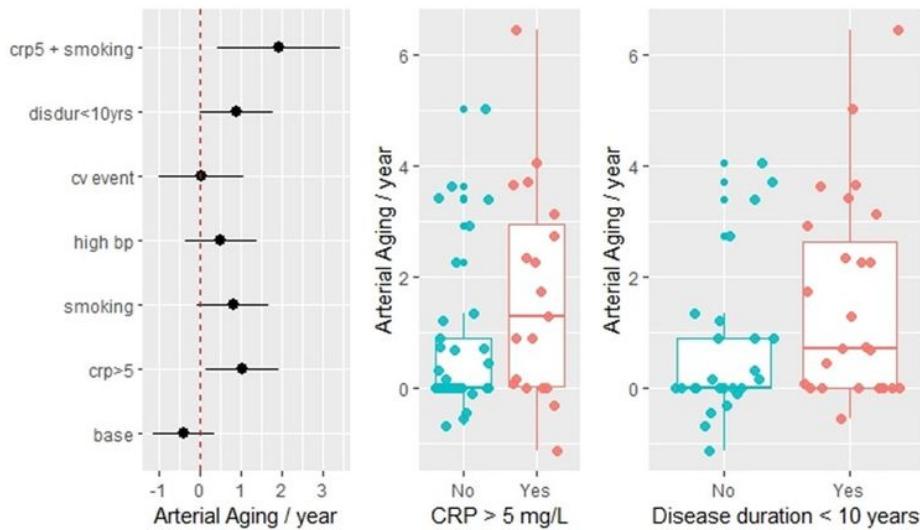
**Figure 2**

Smoking, CV events and hypertension are associated with increased Artage\_dif. Six binary variables were screened for potential effect on Artage\_dif. The arterial age is increased significantly in patients who are smokers, have history of cardiovascular disease (CV event) or who are taking antihypertensive medicines (High BP). The corresponding p values (Kruskall – Wallis test): 0.016 (Smoking), 0.029 (CV event), 0.023 (High BP). Plots where the variable effects were significant are colored while where the effect was not significant are in black (ACCP – anti- cyclic citrullinated peptides antibody, RF – rheumatoid factor).



**Figure 3**

The arterial age difference depends on the disease duration. The effect of disease duration on the arterial age difference between RA patients and controls are shown. The smoothed curve in the left figure was obtained with Lowess. On the right figure the red line represents the fitted regression line. The slope of the regression line (slope = 0.395, t=2.74, p=0.007) is the yearly divergence rate from the control. In both cases the shaded areas around the lines are the 95% confidence intervals. The arterial aging is approximately 40% accelerated.



**Figure 4**

Follow-up data: the effect of inflammation, CV diseases, smoking and RA disease duration on the arterial aging. The arterial aging rate was calculated by dividing the difference of the two consecutive arterial age estimates with the time interval between the two measurements. The left panel shows least-square estimates of five risk factors on the rate: smoking, disease duration  $\leq 10$  years (disdur<10), history of cardiovascular disease (cvevent), CRP  $> 5\text{mg/L}$ , and concomitant antihypertensive drug taking (bp\_high). When the 95% confidence intervals do not cross zero then the effects are significant which is true only for crp5 ( $p = 0.024$ ) and disdur<10 ( $p = 0.05$ ). In absence of any risk factors (which includes that the disease started more than 10 years ago) the aging rate is close to zero (base). The combined effect of two risk factors such as CRP and smoking shown in the figure is an estimated marginal effect. The two boxplots illustrate the effect of crp5 and disdur<10.

## Supplementary Files

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