

## Pattern of cardiovascular diseases among Nigerians with rheumatoid arthritis

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### Abstract

**Background:** Rheumatoid arthritis (RA) is a common chronic inflammatory disease. Cardiovascular disease is one of the most critical extra-articular features, responsible for about half of all deaths in patients with rheumatoid arthritis. This study aims to describe the pattern of cardiovascular diseases among Nigerians with RA.

**Methods:** A two-year cross-sectional study of 101 consecutive RA patients at the Jos University Teaching Hospital, Jos. Clinical, electrocardiography, and echocardiography assessments of the cardiovascular system were performed.

**Results:** The median age (IQR) of the participants was 50(21) years, 82 (81.2%) females and 19 (18.8%) males. The frequency of cardiovascular disease is 72 (71.3%); specifically, hypertension 55(54.5%), hypertensive heart disease 17(16.8%), electrocardiographic abnormalities 45(44.6%) and echocardiographic abnormalities 40 (39.6%). Age (P = 0.02), sex (P = 0.05), occupation (P = 0.02), synovitis (P = 0.03), seropositivity (P = 0.03) and DAS28ESR (P = 0.06) were associated cardiovascular diseases.

**Conclusion:** The prevalence of cardiovascular disorders in Nigerians with RA is high, encompassing a wide range of abnormalities. These abnormalities are higher among the older age group and those with higher disease activity scores.

## Schéma des maladies cardiovasculaires chez les Nigériens atteints de polyarthrite rhumatoïde

### Resume

**Contexte:** La polyarthrite rhumatoïde (PR) est une maladie inflammatoire chronique courante. Les maladies cardiovasculaires sont l'une des caractéristiques extra-articulaires les plus critiques, responsables d'environ la moitié de tous les décès chez les patients atteints de polyarthrite rhumatoïde. Cette étude vise à décrire le profil des maladies cardiovasculaires chez les Nigériens atteints de PR.

**Méthodes:** Une étude transversale de deux ans portant sur 101 patients atteints de PR consécutifs à l'hôpital universitaire de Jos, à Jos. Des évaluations cliniques, électrocardiographiques et échocardiographiques du système cardiovasculaire ont été réalisées.

**Résultats:** L'âge médian (IQR) des participants était de 50 (21) ans, 82 (81,2 %) de femmes et 19 (18,8 %) d'hommes. La fréquence des maladies cardiovasculaires est de 72 (71,3 %) ; plus précisément, l'hypertension 55 (54,5 %), la cardiopathie hypertensive 17 (16,8 %), les anomalies électrocardiographiques 45 (44,6 %) et les anomalies échocardiographiques 40 (39,6 %). L'âge (P=0,02), le sexe (P=0,05), la profession (P=0,02), la synovite (P=0,03), la séropositivité (P=0,03) et le DAS28ESR (P=0,06) étaient des maladies cardiovasculaires associées.

**Conclusion:** La prévalence des troubles cardiovasculaires chez les Nigériens atteints de PR est élevée et englobe un large éventail d'anomalies. Ces anomalies sont plus élevées chez les personnes plus âgées et chez celles ayant des scores d'activité de la maladie plus élevés.

## **INTRODUCTION**

Rheumatoid arthritis is a common chronic inflammatory disease, affecting about 0.24 - 1% of the global population. (1). The disease was initially thought to be absent in Nigerians, but recent reports have shown similar prevalence with the global burden of the disease (2,3).

The peak age of occurrence of RA is around 55 – 64 years for women and 65 – 75 years for men. (4) The prevalence of RA is generally thought to be higher in females than males, with an estimated female-to-male ratio of between 2:1 and 3:1. (5) Rheumatoid arthritis has not shown clear racial bias in its prevalence, as some studies have reported lower prevalence in blacks compared to Caucasians, while others have shown no difference in prevalence between blacks and Caucasians (6).

Cardiovascular disease is one of the most essential extra-articular features of rheumatoid arthritis. It is responsible for about half of all deaths in patients with rheumatoid arthritis in Europe and America (7,8). The increased cardiovascular mortality seen in RA is mainly due to ischemic heart diseases, including acute coronary syndromes, myocardial infarction and congestive cardiac failure, compared to other forms of cardiac death.

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality worldwide, most of which occur in low and medium-income countries (LMIC). There has been a rise in the actual number of CVD-related deaths in LMIC at the same time that the number of deaths from CVD in high-income countries is falling. West African countries are among those with the highest prevalence of CVD-related deaths, and Nigeria has an estimated proportional mortality of 12% attributable to cardiovascular diseases (9). Despite the declining proportion of deaths attributable to CVD in most regions of the world, it remains one of the leading causes of mortality, prompting the World Health Organization (WHO) to include it as one of the targets of Goal 3 in the sustainable development goals indicators.

Several studies in developed nations have documented a higher prevalence of cardiovascular diseases in subjects with rheumatoid arthritis than in the general population. Higher rates of heart failure, cardiac arrest and peripheral vascular diseases have been reported in rheumatoid arthritis patients compared to the general population. (10) There are no studies outlining the prevalence and

pattern of cardiovascular diseases in this population in Nigeria. This study was, therefore, designed to fill this gap.

## **MATERIALS AND METHODS**

### **Study design and setting**

This was a hospital-based cross-sectional descriptive study carried out in the rheumatology clinic of the medical outpatient department of Jos University Teaching Hospital (JUTH). JUTH is the only accredited postgraduate rheumatology training institution in North Central Nigeria. There are five other such centres across the country.

Before the study commenced, an ethical approval with clearance number JUTH/DCS/ADM/127/XXVII/800 was obtained from the human research ethics committee of the Jos University Teaching Hospital. Written informed consent was also obtained from the participants. The study was carried out in full compliance with the principles of the Helsinki Declaration.

### **Study participants**

Rheumatoid arthritis patients who were 18 years and above, fulfilling the revised 2010 American College of Rheumatology (ACR) / European League Against Rheumatism (EULAR) criteria for the classification of rheumatoid arthritis (4) and attending the rheumatology clinic of JUTH with at least one follow-up visit after the diagnosis of rheumatoid arthritis were included in the study. Patients with other autoimmune diseases, rheumatoid arthritis overlap syndromes and other comorbidities that have a direct impact on the cardiovascular system, such as chronic liver disease and hyper or hypothyroidism, were excluded. The estimated minimum sample size for the study was 80, using the sample size calculation for an infinite population with a finite correction (11)

### **Study procedure**

A proforma was designed to obtain information on socio-demographic data, cardiovascular symptoms, and the range of treatments used, including antirheumatic drugs. The questionnaire was administered by a trained research assistant, who also ensured that patients carried out the appropriate investigations. Health Assessment Questionnaire (HAQ), graded from 0, no disability, to 3, severe disability, was used to assess the activities of daily living and a functional disability index (FDI) was calculated from the HAQ scores. A general, rheumatic and

cardiovascular examination was performed on all participants. Weight was recorded in kilograms to the nearest 0.1kg. Height was measured to the nearest 0.01 meter. The body mass index (BMI) was calculated from weight in kilograms (kg) divided by the height in meters squared (m<sup>2</sup>). The tender joint counts, swollen joint counts and the Clinical Disease Activity Index (CDAI) score were estimated for each patient. Pulse rate and blood pressure were measured after five minutes of rest. The blood pressure was measured using a mercury sphygmomanometer in a sitting position with the arm at the level of the heart. Systolic BP was recorded at phase one of the Korotkoff sound, and diastolic BP was recorded at phase five. All peripheral and central pulses were assessed; the cardiac apex and heart sounds were also documented.

Twelve-lead electrocardiography was done for those without a recent result using a GE Medical Systems Information Technologies MAC 1200 ST v.1.2 ECG machine by the ECG technician; AG reported all tracings. Echocardiography was done for those without an acceptable or recent result using an Aloka SSD-3500 echocardiography machine with a 2.5-3.5 MHz transducer probe. Two-dimensional, M-Mode, pulsed-wave, continuous wave and colour Doppler echocardiography assessments were done. Cardiac measurements were done using the American Society of Echocardiography guidelines of leading-edge as measurement points. Complete blood count, erythrocyte sedimentation rate, Rheumatoid factor, and antibody to cyclic citrullinated peptide were recorded, and the Disease Activity Score 28 (DAS28) was estimated for each patient.

### **Statistical analysis**

STATA IC 14.2 by StataCorp LLC, Texas, USA, for Macintosh Operating Systems was used to analyse the data. Continuous variables were expressed as median with interquartile range since a Shapiro-Wilk test shows the data was not normally distributed. Non-continuous variables were expressed as proportions. The chi-squared test was used to determine the significance of the association between the patient's characteristics and the presence or absence of cardiovascular diseases; factors with statistically significant associations with CVD were used in a logistic regression to determine independent associations with CVD. A  $P$ -value  $< 0.05$  was considered statistically significant.

### **RESULTS**

A total of 101 patients who met the inclusion criteria participated in the study, 82 (81.2%) females and 19 (18.8%) males, with a median (IQR) age of 50(21) years. Most of the participants were married, 77(76.2%), formally employed, 44 (43.5%), with tertiary education 57 (56.4%) and no history of alcohol consumption 83 (82.2%) nor cigarette smoking 92 (91.1%). Table 1.

As shown in Table 2, the median (IQR) duration of RA in this population was 4.0 (5.0) years, with a median (IQR) functional disability index (FDI) of 0.8 (1.2) and a median (IQR) disease activity score 28 ESR of 4.1 (2.2).

Figure 1 shows that 44 (43.6%) of the study participants developed deformities, 20 (19.8%) stopped working because of RA, 12 (11.9%) needed an assistive device, 18 (17.8%) required help from other people to carry out their daily functions, 26 (25.7%) had x-ray features of RA and 69 (68.3%) were seropositive.

The overall frequency of cardiovascular disease in the study population is 72 (71.3%); specifically, hypertension 55(54.5%), hypertensive heart disease 17(16.8%), electrocardiographic abnormalities 45(44.6%) and echocardiographic abnormalities 40 (39.6%) etc. Table 3.

Age ( $\chi^2$  9.02,  $P = 0.02$ ), sex ( $\chi^2$  3.78,  $P = 0.05$ ), occupation ( $\chi^2$  9.26,  $P = 0.02$ ), synovitis ( $\chi^2$  4.45,  $P = 0.03$ ), seropositivity ( $\chi^2$  4.68,  $P = 0.03$ ) and DAS28ESR ( $\chi^2$  12.5,  $P = 0.006$ ) had statistically significant association with cardiovascular diseases on bivariate analysis, Table 4. As shown in Table 5, older age (OR 14.03, 95% CI 1.20 – 163.84,  $P = 0.03$ ), formal employment (OR 2.68, 95% CI 1.12 – 3.32,  $P = 0.01$ ) and High Disease Activity (OR 7.28, 95% CI 1.28 – 41.0,  $P = 0.02$ ) were independently associated with cardiovascular disease on logistic regression even though the confidence interval for older age appeared unreliable. Figure 2 shows the adjusted predictions of cardiovascular disease at different disease activities interacting with the age of the participants.

### **DISCUSSION**

The prevalence of cardiovascular diseases in this population of rheumatoid arthritis patients was high, with 71.3% of the patients having at least one form of cardiovascular disease. This is higher than the 37.0%, 18.5% and 26.3% reported among general medical patients in South Western, South Eastern & North Western Nigeria, respectively. (12-14) This finding

supports the hypothesis that there is an excess of cardiovascular diseases in patients with rheumatoid arthritis compared to the general population.

The prevalence of cardiovascular diseases in this study is also higher than the 35.3%, 50% and 60% found in Latin American and Scandinavian populations with rheumatoid arthritis, respectively, all of which were higher than the prevalence in their respective general populations. (15, 16) This further suggests that Nigerians with rheumatoid arthritis share a higher prevalence of cardiovascular diseases than the general population that has been established in other populations.

Similar to the findings of Adedapo AD (12) in Southwestern Nigeria, hypertensive heart disease was the predominant form of cardiovascular disease in this study. This may be attributable to the ongoing epidemiological transition in the developing world. (13) The African region of the World Health Organization has been shown to have the highest burden of hypertension, with a prevalence of 46%, similar to the 54% obtained in this study. (17) This is higher than the overall prevalence of 28.9% in a meta-analysis of publications on hypertension in Nigeria. (18) The prevalence of hypertension in this population of RA patients is similar to that in RA patients compared to the general population from other studies. In Greece, the prevalence of hypertension in RA patients was 54% compared to 34% in age and sex-matched non-RA controls, while in the United States, the prevalence was 34% vs. 23.4%. (19,20) This higher prevalence of hypertension in RA patients has been attributed to chronic inflammation, physical inactivity, and drugs used to treat RA. (19,20)

Cardiomyopathies in this study (2%) were more common than the <1% reported by Adedapo AD (16) but similar to the 3-30% that has been reported among rheumatoid arthritis patients in other populations. (21) The increased prevalence has mainly been attributed to myocarditis from chronic inflammation and drugs like non-steroidal Anti-inflammatory drugs, corticosteroids and hydroxychloroquine. (21)

Earlier reports from echocardiographic and postmortem series considered pericardial disease the commonest cardiac manifestation of RA, but more recent studies suggest the contrary (21,22). The declining prevalence of pericarditis among RA patients may be attributable to earlier diagnosis and more effective treatment. However, the 5% prevalence of pericardial disease recorded in this study is higher than the

3.3% reported by Ogah et al. among heart failure patients in South Western Nigeria. (23) and the cumulative prevalence of 1.8% and 1.1% among all cardiac patients with echocardiography in Nigeria and Africa, respectively (24).

The prevalence of left ventricular diastolic dysfunction in our RA population (15.8%) is higher than the 11.3% of the general population reported by Adamu et al. (25). Higher prevalence of left ventricular diastolic dysfunction in RA patients compared to non-RA patients has been linked to a longer duration of RA, higher ESR, higher disease activity and seropositivity, which may be indicative of the impact of chronic inflammation on the myocardium. (26)

The variation in the diagnosis of Left ventricular hypertrophy (LVH) by electrocardiography and echocardiography is an evolving area of understanding requiring more studies. Even though echocardiography is considered the gold standard in diagnosing LVH, ECG LVH may differ from echo LVH. However, factors such as age, sex, body habitus and even differences in the time of performance of either test can influence the result. The prevalence of ECG LVH in our study was higher (22%) than echo LVH (9%). The ECG LVH in our RA population is higher than reported among hypertensive (16.5%) and normotensive (13%) individuals in Port Harcourt, South-South Nigeria. (27) However, our echo LVH is lower than 18.2% (normotensive), 20.8% (uncontrolled hypertensives) and 24.1% (controlled hypertensives) reported by Salako et al. in Ibadan South West Nigeria. (28) It is also lower than the 16% reported among RA patients in the United States of America and was associated with older age and obesity. (29) This may be because the participants in their study were less obese and older than our population, given that poor acoustic window and attenuation artefact limits echocardiographic findings in obesity, while LVH on echocardiography is known to be more prevalent with age.

Left Atrial Enlargement is associated with atrial fibrillation, heart failure and cardiovascular events in patients with RA. The frequency of LAE in our population is similar to the 14% reported by Galarza-Delgado et al. (30) in their RA patients, even though our patients were diagnosed on ECG while theirs were diagnosed by echocardiography.

Other cardiac abnormalities reported among our RA patients included heart failure, right and left bundle branch block, right ventricular hypertrophy, aortic dilation and

valvular heart disease, all of which have been documented in other populations. (21). Also, similar to previous reports, the cardiac abnormalities reported amongst our patients were more common in the older age group and those with higher disease activity. However, unlike studies on cardiovascular event risk, other RA-specific factors, including disease duration and inflammatory and serologic markers, were not significantly associated with the cardiac abnormalities observed in this population. (8) More studies with larger sample sizes and comparative arms may be needed to study this relationship in our population.

**Limitations:** Limitations of the study include its cross-sectional study design, conducted in a single centre without a control group. However, we have attempted to document the pattern of cardiovascular abnormalities among Nigerians with RA using standard evaluation tools like ECG and echocardiography.

#### CONCLUSION AND RECOMMENDATION

Rheumatoid arthritis patients in our population have a high frequency of cardiovascular disorders encompassing a wide range of abnormalities. These abnormalities are detected more with echocardiography and are higher among the older age group and those with higher disease activities. Therefore, RA patients should be regularly assessed for cardiovascular abnormalities using this modality.

**Author's contribution:** All authors reviewed and approved the manuscript for publication. CUU was involved in the conception, data collection, data analysis and writing of the manuscript. CAM was involved with the conception, data collection and writing of the manuscript. GAA was involved in the conduction and interpretation of the ECG and ECHO and writing of the manuscript. FOT was involved in the manuscript's conception, analysis and writing.

**Conflict of interest:** The authors declare no conflicts of interest.

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**Table 1. Sociodemographic characteristics of the study participants**

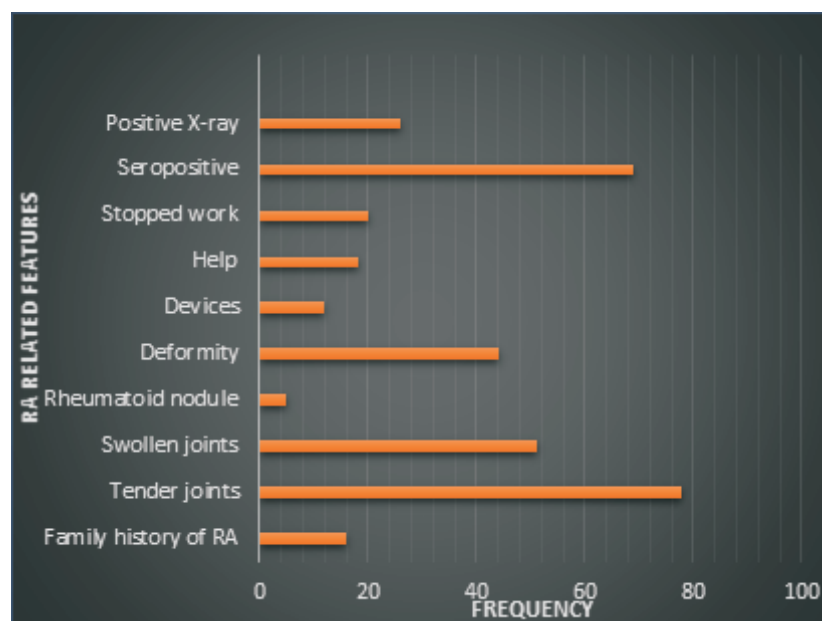
Variable	Frequency (%), n = 101
Sex	
Females	82.0 (81.2)
Males	19.0 (18.8)
Marital status	
Single	13 (12.9)
Married	77 (76.2)
Divorced	01 (01.0)
Widowed	10 (09.9)
Educational attainment	
None	19 (18.8)
Primary	11 (10.9)
Secondary	14 (13.9)
Tertiary	57 (56.4)
Occupation	
Unemployed	34 (33.7)
Informal	12 (11.9)
Formal	44 (43.5)
Retired	11 (10.9)
Habits	
Smoking	09 (08.9)
Takes alcohol	18 (17.8)

% = Percentage, n = number of participants

**Table 2. Characteristics of RA in the study population**

Variable	Median (IQR)
Duration of RA in years	4.0 (5.0)
Health Assessment Questionnaire (HAQ) score	7.0 (9.0)
Functional Disability Index (FDI)	0.8 (1.2)
Erythrocyte Sedimentation Rate (ESR)	56.0 (51.0)
Rheumatoid Factor	45 (141.4)
Antibody to Cyclic citrullinated Peptide (ACCP)	60.3 (176.6)
Disease Activity Score 28 (DAS28ESR)	4.1 (2.2)
Clinical Disease Activity Index (CDAI)	9 (13.0)

IQR = Interquartile range



**Figure 1. Frequency of RA related features in the study population**

**Table 3. The pattern of cardiovascular diseases in RA patients**

<b>Cardiovascular diseases</b>	<b>Frequency (%), n=72 (71.3)</b>
<b>Clinical</b>	
Hypertension	55 (54.5)
Hypertensive heart disease	17 (16.8)
Heart failure	1 (1.0)
<b>Electrocardiography</b>	
Left axis deviation	8 (7.9)
Left atrial enlargement	13 (12.9)
Left ventricular hypertrophy	22 (21.8)
Right ventricular hypertrophy	1 (1.0)
Right bundle branch block	1 (1.0)
Left bundle branch block	1 (1.0)
Premature ventricular contraction	2 (2.0)
Pericarditis	5 (5.0)
<b>Echocardiography</b>	
Diastolic dysfunction	16 (15.8)
Dilated cardiomyopathy	2 (2.0)
Aortic dilatation	1 (1.0)
Valvular disease	1 (1.0)
Septal hypertrophy	2 (2.0)
Left ventricular hypertrophy	9 (8.9)
Pericarditis	5 (5.0)
Hypertensive heart disease	6 (5.9)

% = Percentage, n = number of participants with cardiovascular diseases.

**Table 4. Association between patient characteristics and cardiovascular diseases**

<b>Variable</b>	<b>Cardiovascular disease</b>		$\chi^2$	<b>P value</b>
	<b>Yes = 72</b>	<b>No = 29</b>		
<b>Age groups in years, n (%)</b>			<b>9.02</b>	<b>0.02*</b>
≤35	<b>11 (15.3)</b>	<b>10 (34.5)</b>		
<b>36-50</b>	<b>22 (30.5)</b>	<b>08 (27.6)</b>		
<b>51-65</b>	<b>21 (29.2)</b>	<b>10 (34.5)</b>		
≥66	<b>18 (25.0)</b>	<b>01 (3.4)</b>		
<b>Sex, n (%)</b>			3.78	0.05*
Male	17 (23.6)	02 (6.9)		
Female	55 (76.4)	27 (93.1)		
<b>Marital status, n (%)</b>			2.76	0.42*
Single	08 (11.1)	05 (17.2)		
Married	54 (75.0)	23 (79.3)		
Divorced	01 (1.4)	00 (0.0)		
Widowed	09 (12.5)	01 (3.5)		
<b>Education, n (%)</b>			5.10	0.16*
None	12 (16.7)	06 (20.7)		
Primary	11 (15.3)	00 (0.0)		
Secondary	09 (12.5)	05 (17.2)		
Tertiary	40 (55.5)	18 (62.1)		
<b>Occupation</b>			9.26	0.02*
Formal	34 (47.2)	10 (34.5)		
Informal	08 (11.1)	04 (13.8)		
Unemployed	19 (26.4)	15 (51.7)		
Retired	11 (15.3)	0 (0.0)		
<b>Smoking</b>	07 (9.7)	01 (3.5)	0.11	0.29*
<b>Diabetes Mellitus</b>	06 (8.3)	0 (0.0)	2.56	0.10*
<b>Family history of CVD</b>	19 (26.4)	06 (20.7)	0.36	0.54
<b>Obesity</b>	19 (26.4)	05 (17.2)	0.95	0.32

\*Fisher's Exact test,  $\chi^2$  = Chi-Square, CVD = Cardiovascular disease



**Table 5. Association between RA specific factors and cardiovascular diseases**

Variable	Cardiovascular disease		$\chi^2$	P value
	Yes = 72	No =29		
RA duration			3.96	0.13*
< 5 years, n (%)	45 (63.4)	15 (51.7)		
5-10 years, n (%)	16 (22.5)	12 (41.4)		
≥10 years, n (%)	10 (14.1)	2 (6.9)		
Family history of RA, n (%)			1.44	0.48*
Yes	12 (16.7)	04 (23.8)		
No	57 (79.1)	25 (86.2)		
Unknown	03 (4.2)	0 (0.0)		
Functional Disability, n (%)			2.65	0.44*
Mild	35 (48.6)	19 (65.5)		
Moderate	30 (41.7)	08 (27.6)		
Severe	06 (8.3)	02 (6.9)		
Very severe	01 (1.4)	0 (0.0)		
Synovitis, n (%)	41 (57.7)	10 (34.5)	4.45	0.03
Deformity	30 (42.3)	14 (48.3)	0.30	0.58
Rheumatoid Nodule	5 (7.0)	0 (0.0)	2.14	0.14*
Elevated ESR, n (%)	59 (81.9)	21 (72.4)	1.14	0.28
Seropositive RA, n (%)	57 (79.2)	28 (96.5)	4.68	0.03*
Positive X-ray findings, n (%)	16 (22.2)	10 (34.5)	1.62	0.20
DAS28, n (%)			12.5	0.006*
Remission	06 (8.3)	07 (24.1)		
Low disease activity	07 (9.7)	03 (10.3)		
Moderate disease activity	18 (25.0)	13 (44.8)		
High disease activity	41 (57.0)	06 (20.7)		

\*Fisher’s Exact test,  $\chi^2$  = Chi-Square, RA= Rheumatoid Arthritis, n = number of participants, % = Percentage, ESR = Erythrocyte Sedimentation Rate, DAS28 = Disease Activity Score 28

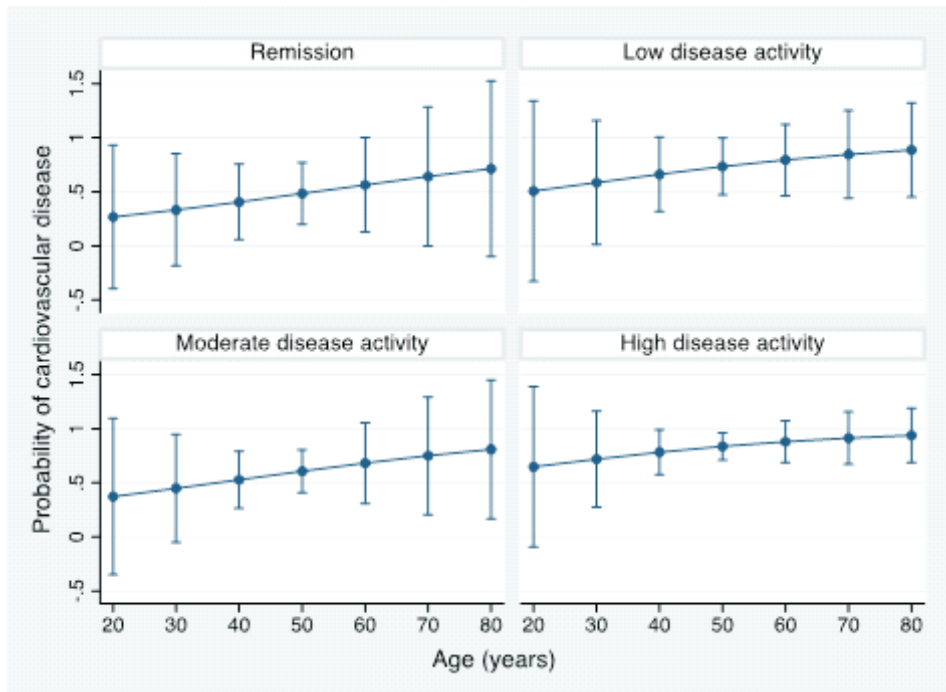
**Table 6a. Predictors of Cardiovascular diseases using Logistic regression (composite)**

Cardiovascular disease	Odds ratio	95% confidence interval	P value
<b>Age</b>	<b>1.80</b>	<b>1.03 – 3.13</b>	<b>0.03</b>
<b>Sex</b>	<b>0.44</b>	<b>0.07 – 2.59</b>	<b>0.36</b>
<b>Occupation</b>	<b>1.93</b>	<b>1.12 – 3.32</b>	<b>0.01</b>
<b>seropositivity</b>	<b>0.23</b>	<b>0.02 – 2.19</b>	<b>0.20</b>
<b>DAS28 Disease activity</b>	<b>1.88</b>	<b>1.10 – 3.19</b>	<b>0.01</b>

**Table 6b. Predictors of Cardiovascular diseases using Logistic regression (margins)**

Variable	Odds ratio	95% confidence interval	P value
Age groups (years)			
≤35	1		
36-50	1.71	0.38 – 7.73	0.48
51-65	1.89	0.45 – 7.83	0.37
≥66	14.03	1.20 – 163.84	0.03
Sex			
Male	1		
Female	0.52	0.08 – 3.24	0.48
Occupation			
Unemployed	1		
Informal	1.57	0.39 – 6.26	0.51
Formal	2.68	1.12 – 3.32	0.01
Disease Activity			
Remission	1		
LDA	3.60	0.50 – 25.96	0.20
MDA	1.75	0.33 – 9.23	0.50
HDA	7.28	1.28 – 41.01	0.02
Seropositive	0.25	0.27 – 2.42	0.23
Synovitis	1.80	0.55 – 5.86	0.32

1= Reference



**Figure 2. Adjusted predictions of cardiovascular disease at different disease activity**

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