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Sitting time is negatively related to microvascular endothelium-dependent function in Rheumatoid Arthritis

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Author contributions: SF, JvVZ and GK conceived the idea for the manuscript. AS collected the data, supervised by GK, JvVZ and GM. SF prepared and analysed the data, and wrote the first draft of the manuscript. All authors (SF, AS, GM, JD, GK JvVZ) revised and contributed to subsequent versions of the manuscript to produce the final draft

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1 Abstract

2 **Background:** Sedentary behaviour is linked to increased cardiovascular disease risk in
3 Rheumatoid Arthritis (RA), but the biological processes underlying this relationship are not
4 understood. **Objectives:** To investigate the cross-sectional associations of habitual sedentary
5 behaviour, with endothelial function in RA. **Methods:** Sixty-eight RA patients ($M_{age} = 55 \pm 12$
6 years) underwent Laser Doppler Imaging with iontophoresis, to assess microvascular
7 endothelium-dependent (acetylcholine, ACh) and endothelium-independent (sodium
8 nitroprusside, SNP) function. Large-vessel endothelium-dependent and endothelium-independent
9 functions were measured via flow-mediated dilation (FMD) and glyceryl trinitrate dilation (GTN),
10 respectively. Habitual sedentary behaviour (hours/week sitting) was self-reported (International
11 Physical Activity Questionnaire). **Results:** Regressions revealed sitting time significantly
12 negatively predicted microvascular endothelium-dependent function ($ACh, \text{unstandardized}\beta = -3.25, p$
13 $= .02, 95\% \text{ CI } [-6.07, -.42], R^2 = 0.06$), but did not associate with other endothelial function
14 outcomes (SNP, FMD, GTN). **Conclusion:** Habitual sitting time appears to be adversely linked to
15 microvascular endothelium-dependent function among people living with RA.

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17 **Keywords:** Sedentary behaviour; Rheumatoid arthritis; Endothelial function; Cardiovascular
18 disease; Ultrasonography.

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1 Introduction

2 Cardiovascular disease (CVD)¹ is the leading cause of death among people living with
3 Rheumatoid Arthritis (RA) [1], with RA increasing CVD risk by ~50% compared to the
4 general population [2]. High levels of sedentary behaviour (*waking behaviour* ≤ 1.5 metabolic
5 equivalents, *whilst sitting/lying*) are linked to increased CVD risk in RA, independently of the
6 benefits of physical activity [3]. Whilst the biological mechanisms underlying this adverse
7 relationship are not yet known, recent experimental work suggests endothelial dysfunction
8 may play an important role [4].

9 The endothelium maintains vascular homeostasis by regulating vascular tone and anti-
10 atherosclerotic processes via the release of vasodilator molecules, such as nitric oxide (NO),
11 prostacyclin (PGI₂) and endothelium derived hyperpolarizing factor (EDHF) [5]. Several
12 non-invasive assessments of NO-mediated vasodilation (i.e., endothelium-dependent
13 function) can be conducted in the microvessels and large-vessels, and provide early indication
14 of future CVD risk in the general population [6]. RA patients also have endothelial
15 dysfunction which likely results from subtle interactions between inflammation and classical
16 CVD risk factors [7], adversely affecting downstream endothelium-independent vasodilatory
17 processes (i.e., smooth muscle cell integrity). [5] Indeed, RA patients exhibit poor
18 microvascular perfusion in the coronary circulation, even when the larger epicardial arteries
19 are clear, which suggests that different vascular beds are affected differently by RA-related
20 factors [8]. However at present, it is not clear which factors affect the specific vascular
21 outcomes in RA (i.e., endothelium-dependent vs. independent function in the small vs. large-
22 vessels), and identification of such factors (e.g., the role of sedentary behaviour) is necessary
23 to inform effective CVD prevention in this high-risk population.

24 To date, the majority of research investigating the implications of sedentary behaviour
25 for endothelial function, has employed experimental designs to examine the effects of
26 prolonged sitting (i.e., 3-5 hours uninterrupted sitting in a laboratory) on large-vessel
27 endothelium-dependent function in healthy males [9]. Research investigating the impact of
28 more habitual (daily) sedentariness on microvascular and large-vessel endothelial function is
29 required to better evaluate its role in the development of CVD. This is important to
30 investigate in RA specifically, as the mechanisms that drive vascular dysfunction may differ
31 to those in healthy adults [10].

32 The aim of this study was therefore to examine the cross-sectional associations
33 between habitual sedentary behaviour, with microvascular and large-vessel endothelium-
34 dependent, and endothelium-independent function, in patients with RA. The data presented
35 herein represents secondary analysis of previously published data, reporting associations
36 between CVD risk and endothelial function in this cohort [11].

37 Materials and Methods

38 Ninety-eight RA patients were recruited from Rheumatology outpatient clinics at Russells
39 Hall Hospital (Dudley Group NHS Foundation Trust). All patients recruited met the 1987 RA
40 criteria of the American College of Rheumatology. Informed consent was obtained from all
41 individual participants included in the study. Ethical approval was granted by the local
42 National Health Service Research Ethics Committee (approval number:10/H1206/59).

¹ CVD, cardiovascular disease; RA, Rheumatoid Arthritis; NO, Nitric Oxide; DAS, Disease Activity Score; ESR, Erythrocyte Sedimentation Rate; HAQ, Health Assessment Questionnaire; ACh, Acetylcholine; SNP, sodium nitroprusside; FMD, Flow Mediated Dilation; GTN, Glyceryl-trinitrate.

1 Participants reported to a temperature-controlled vascular laboratory (22°C) to
2 complete assessments, in a fasted state (12-hours) having refrained from exercise for 24hrs.
3 *RA characteristics*; Disease activity was assessed using the Disease Activity Score in 28-
4 joints (DAS28) and erythrocyte sedimentation rate (ESR). Disease severity was measured via
5 the Stanford Health Assessment Questionnaire (HAQ). Use of vasoactive medication (i.e.,
6 anti-hypertensives, beta-blockers and/or calcium channel blockers) was self-reported and
7 corroborated with medical notes.

8 *Global (10-year) CVD risk*; QRISK2 was used to indicate ten-year CVD risk. QRISK2 score
9 was calculated using participants; age, gender, height, weight, blood pressure, cholesterol
10 (total/HDL ratio), smoking status, diabetic status, presence of kidney disease and family
11 history of heart disease [11].

12 *Endothelial function*; First, microvascular endothelial function was assessed non-invasively in
13 the forearm, using Laser Doppler Imaging with iontophoresis of 1% Acetylcholine (ACh,
14 endothelium-dependent function) and 1% sodium nitroprusside (SNP, endothelium-
15 independent function), in 2.5ml solution containing 0.5% saline, according to previously
16 established guidelines [12]. Following this, large vessel endothelium-dependent (flow
17 mediated dilatation, FMD) and endothelium-independent (sublingual glyceryl-trinitrate,
18 GTN) function, were measured using high-resolution Doppler Ultrasonography of the
19 brachial artery [12]. Assessments of microvascular endothelial function were conducted first,
20 as both FMD and GTN may affect blood flow in the forearm, and therefore iontophoresis
21 measurements. Large vessel endothelium-independent function was assessed last, as
22 administration of GTN causes systemic vasodilation, which would affect all preceding
23 vascular tests.

24 Endothelial function was expressed as the percentage increase in perfusion or diameter
25 from baseline. A single observer conducted all vascular assessments (AS), reporting intra-
26 observer coefficients of variation of 6.5% (ACh), 5.9% (SNP), 10.7% (FMD) and 11.8% for
27 (GTN). Data for ACh/SNP and GTN were not collected from 3 participants due to technical
28 problems with equipment.

29 *Sitting time*; Habitual sitting-time was self-reported using the International Physical Activity
30 Questionnaire (IPAQ). Participants reported their average time spent sitting on; 1) weekdays,
31 and 2) weekend days (i.e., at home, whilst studying, leisure time), over the previous 7-days.
32 Total weekly sitting time (hours/week) was computed; (weekday sitting time x 5) + (weekend
33 day sitting time x 2).

34 Of the initial 98 participants recruited, 30 were excluded on the basis of missing IPAQ
35 data (n = 27, missing data = 28%), or as extreme outliers (ACh/SNP, n = 3). Following these
36 exclusions, missing data were < 5% for; QRISK2 = 2, DAS28 = 2, HAQ = 1, ACh/SNP = 3,
37 GTN = 2). Missing values were therefore imputed to maximise statistical power (expectation
38 maximisation method), retaining a final sample of n = 68 for statistical analyses. Participants
39 in this final sample were not significantly different to those excluded (n = 30) for all targeted
40 variables (Table 1).

41 Cross-sectional associations between habitual sitting time and endothelial function
42 outcomes were examined via multiple regression analyses, in conjunction with bootstrapping.
43 Bootstrap-generated 95% bias-corrected confidence intervals were constructed for 5000
44 samples [13], and analyses were adjusted for RA characteristics, global CVD risk, and
45 vasoactive medication. Bootstrapping is a non-parametric resampling procedure reported to
46 be superior to alternative tests with respect to Type 1 error rates and power (Table 1).[13]
47 Analysis was performed using SPSS (version 24.0).

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2 | Results

3 Descriptive statistics are reported in Table 1. The sample was largely female, with moderate
4 disease activity and moderate-to-severe disability. Regression analysis (Table 2) revealed
5 habitual sitting time was significantly negatively related to microvascular endothelium-
6 dependent function (ACh, $\text{unstandardized}\beta = -3.25, p = .02$), but not microvascular endothelium-
7 independent function (SNP, $\text{unstandardized}\beta = -1.94, p = .07$). Sitting time accounted for 6% of
8 the variance in microvascular endothelium-dependent function, with the total model
9 explaining 18% of the variance in this outcome. Habitual sitting time did not significantly
10 predict large-vessel endothelium-dependent vasodilation (FMD, $\text{unstandardized}\beta = .01, p = .84$) or
11 independent vasodilation (GTN, $\text{unstandardized}\beta = -.06, p = .37$).

12 Discussion

13 This is the first study to reveal that higher self-reported sitting time is predictive of impaired
14 microvascular endothelium-dependent function among people with RA. This cross-sectional
15 association was observed after adjusting for global CVD risk, RA characteristics and
16 vasoactive medication. Results provide new evidence to suggest “too much sitting” may be
17 linked to poorer endothelial function, and contribute toward increased CVD risk in RA [1, 3].

18 A recent experimental study in healthy males reported significantly reduced
19 hyperaemic response in the microvessels, but not the large-vessels of the brachial artery,
20 following 6-hours of uninterrupted sitting [14]. Our results build on this work, to suggest that
21 habitual sedentary [i.e., repeated episodes of prolonged (uninterrupted) sitting], may lead to
22 chronic impairments in peripheral microvascular endothelium-dependent function among
23 people living with RA. In addition, these data strengthen the suggestion that the peripheral
24 microvasculature may be more vulnerable to the adverse consequences of sedentary
25 behaviour, relative to the large-vessels.

26 Reduced blood flow and associated shear rate are the mechanisms proposed to
27 underlie the association between sitting and microvascular endothelium-dependent
28 dysfunction. That is, in the absence of muscle activation (e.g., during low-energy sitting),
29 peripheral vascular blood flow and shear rate are reduced [14], which in turn may lead to
30 reduced NO bioavailability, and reduced vasodilatory function of the microvasculature [4, 9,
31 14]. Through such mechanisms, high levels of sitting time may perpetuate an already
32 unfavourable CVD profile, and further contribute towards promoting vascular dysfunction
33 and cardiovascular co-morbidity in RA. Indeed, vascular dysfunction in the peripheral
34 circulation is reported to be a good predictor of long-term cardiovascular events in individuals
35 with atherosclerosis, and healthy older participants [15, 16].

36 The impact of sitting on microvascular but not large-vessel endothelial function could
37 be due to the microvessels comprising the largest proportion of the vasculature [17]. Thus, the
38 microvasculature is likely to have greater exposure to damaging stimuli - e.g., the
39 physiological processes associated with sedentary behaviour. As such, repeated episodes of
40 sedentary behaviour may compromise the function of the microvessels, prior to (and to a
41 greater extent than), any observed impairments in the large-vessels. Indeed, microvascular
42 abnormalities can occur before, or alongside the development of CVD risk factors in healthy
43 individuals, and among those with hypertension [18-20]. Coronary microvascular disease is
44 also apparent in the absence of large-vessel disease in RA [8].

45 Our study did not demonstrate associations between habitual sitting time and
46 endothelium-independent microvascular and large-vessel function in RA. This may suggest
47 that the adverse effects of sitting relate primarily to the functionality of the endothelial cells

1 themselves (i.e., NO availability), rather than the integrity of the smooth muscle cells to relax
 2 [5]. However, this study reports secondary analysis of an existing data set, which may be
 3 underpowered to detect such associations. Indeed, standardised effect sizes were comparable
 4 for endothelium-dependent and endothelium-independent microvascular function outcomes
 5 (Table 2 legend). Thus, studies designed specifically to assess the role of sitting for
 6 endothelium-independent function in RA are required. Other limitations to this study include
 7 a cross-sectional design and a reliance on self-reported sedentary behaviour. Larger
 8 prospective and experimental studies utilising objective measurement devices are therefore
 9 required to confirm current findings. Insights regarding the specific mechanisms by which
 10 sitting time may lead to endothelial dysfunction in RA may be provided by experimental
 11 studies that compare this clinical population with healthy controls.

12 In conclusion, habitual self-reported sitting time appears to be associated with
 13 microvascular endothelium-dependent function in people with RA, but not large-vessel
 14 endothelial function. Results highlight the importance of experimental studies to confirm
 15 whether sedentary behaviour represents a modifiable risk factor for CVD in RA.

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Table 1. Descriptive statistics

	Mean \pm SD n = 68	Range (min – max)
Age (years)	55 \pm 12	24 – 77
Gender (% female)	74%	
Height (cm)	164.0 \pm 9.3	142.0 – 190.0
Weight (kg)	80.8 \pm 18.2	48.7 – 122.9
RA characteristics		
Disease activity (DAS28)	3.56 \pm 1.37	0.14 – 7.00
[¶] Disease severity (HAQ)	1.59 \pm 0.88	0 – 3
Vasoactive medication (% yes)	47%	
CVD risk factors		
Total cholesterol (mmol/L)	4.9 \pm 1.0	3.0 – 7.1
HDL cholesterol (mmol/L)	1.4 \pm .35	0.8 – 2.4
Systolic blood pressure (mmHg)	130 \pm 17	93 – 165
Diastolic blood pressure (mmHg)	80 \pm 10	58 – 105
Body-mass-index (kg/m ²)	30.2 \pm 6.4	20.3 – 45.9
Smoker (% current smokers)	19%	
Diabetes (% yes)	6%	
Kidney Disease (% yes)	2%	
Family history of heart disease (% yes)	47%	
[¶] QRISK2 (%)	18.4 \pm 14.2	0 – 66
Endothelial function		
<i>Microvascular function</i>		
[¶] Endothelium-dependent (ACh)	316 \pm 212	– 3 – 908
[¶] Endothelium-independent (SNP)	302 \pm 180	– 4 – 832
<i>Large-vessel function</i>		
Endothelium-dependent (FMD)	9.4 \pm 5.9	– 1.4 – 23.0
Endothelium-independent (GTN)	22.9 \pm 8.5	4.8 – 44.4
Sitting time		
Weekday (hours)	5.5 \pm 2.8	1.0 – 13.0
Weekend day (hours)	5.8 \pm 2.6	1.5 – 13.0
Total weekly (hours)	38.9 \pm 18.3	10.5 – 91.0

Note: [¶] = Non-normally distributed data (Kolmogorov-Smirnov $p < .05$). Log transformations did not reduce skewness in the case of HAQ. Consequently, non-parametric tests (i.e., Mann-Whitney (M-W) U, bootstrapping) were used in subsequent analyses that included non-normally distributed data.

Data is presented following imputation of missing values for the final sample of $n = 68$ participants included in regression analyses. Participants included were not significantly different from those excluded for; age ($t(92) = -1.20$), gender ($\chi^2(1) = .10$), all endothelial function outcomes (ACh (M-W U = -1.40); SNP (M-W U = -.76); FMD ($t(90) = 1.11$); GTN ($t(89) = .35$), QRISK2 (M-W U = .25), RA characteristics (DAS28 ($t(90) = .13$); HAQ (M-W U = 1.76)), vasoactive medication ($\chi^2(1) = .31$) [all $p > .08$]

Table 2. Results of regression analyses examining associations between self-reported sitting time and endothelial function outcomes.

	ACh				SNP				FMD				GTN			
	β	p	95% CI [upper, lower]	R ²	β	p	95% CI [upper, lower]	R ²	β	p	95% CI [upper, lower]	R ²	β	p	95% CI [upper, lower]	R ²
Model 1																
Global CVD risk (Q-risk2)	-4.81	.02*	-8.62, -1.58	.10	-2.03	.28	-5.83, 1.16	.01	-.11	.13	-.24, .01	.05	-.25	.00**	-.36, -.14	.24
Disease activity (DAS28)	20.75	.26	-13.67, 55.50	.02	7.74	.68	-25.45, 48.00	.01	.44	.52	-.91, 1.61	.01	-.25	.79	-2.13, 1.38	.00
Disease severity (HAQ)	-1.94	.95	-74.37, 58.29	.00	-57.38	.08	-119.42, -1.46	.05	.13	.90	-1.72, 2.21	.00	1.50	.25	-.94, 4.52	.01
Vasoactive medication	-12.68	.79	-111.69, 87.89	.00	-40.96	.32	-117.86, 37.55	.01	-1.30	.30	-3.49, .93	.01	3.83	.04*	.56, 7.16	.05
<i>Total Model 1</i>		.09		.12		.23		.08		.28		.07		.00**		.30
Model 2																
Sitting time (hours/week)	-3.25	.02*	-6.07, -.42	.06	-1.94	.07	-4.32, -.14	.03	.01	.84	-.08, .10	.00	-.06	.37	-.17, .06	.01
<i>Total Model 2</i>		.03*		.18		.14		.11		.84		.07		.32		.31

Note: RA patients were recruited from Russells Hall Hospital between September 2008 and September 2010

β = bootstrapped path coefficients (unstandardized), * $p < .05$, ** $p < .01$. The 95% bootstrap bias corrected confidence intervals are reported (95% CI [upper, lower]). R² = variance in endothelial function explained by predictor variable. For *Total Model 1*, p = significance of model. For *Total Model 2*, p = significance of R² change.

Model 1 = relationships between global CVD risk, RA characteristics, and vasoactive medication with endothelial function.

Model 2 = associations between total weekly sitting time and endothelial function adjusting for factors in Model 1. Relationships reported in Model 2 were unchanged where non-bootstrapped regressions were computed. Standardised (non-bootstrapped) coefficients for the relationships between sitting time and endothelial function outcomes were; ACh, $\beta = -.28$, $p = .03$; SNP, $\beta = -.20$, $p = .14$; FMD, $\beta = .03$, $p = .84$; GTN, $\beta = -.12$, $p = .32$

CVD = Cardiovascular Disease; DAS28 = Disease Activity Score 28; HAQ = Health Assessment Questionnaire; ACh = Acetylcholine; SNP = Sodium Nitroprusside; FMD = Flow Mediated Dilation; GTN = Glyceryl Trinitrate.