CONCISE REPORT

Patients with regular physical activity before onset of rheumatoid arthritis present with milder disease

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ABSTRACT

Objectives Physical activity has been shown to decrease inflammatory markers; here we investigate the effect on the clinical presentation of rheumatoid arthritis (RA).

Methods We used the cases from the population-based EIRA study (N=617), followed in the Swedish Rheumatology Quality Register, calculating the odds of having above median level of 28-joint disease activity score (DAS28), physician assessment, pain (visual-analogue scale (VAS), VAS-pain) and activity limitation (health assessment questionnaire (HAQ)) at diagnosis, as an effect of physical activity 5 years before diagnosis, investigated both in categories and dichotomised.

Results Dose–response relationships were seen for all measures; the higher the level of physical activity, the lower the likelihood of having outcome measure above median. Further, *regular* physical activity associated with 42% reduced odds of having DAS28 above median (OR=0.58 (95% CI 0.42 to 0.81)). Effects were similar for VAS-pain (OR=0.62 (95%CI 0.45 to 0.86)) and physician assessment (OR=0.67 (95%CI 0.47 to 0.95)) but not for HAQ. Statistically significant effects were also found both for the combined objective components and the combined subjective components of DAS28.

Conclusions Physically active individuals seem to present with milder RA, which adds to the evidence of beneficial effects of physical activity on inflammatory diseases. The observation should be important for both health professionals and individuals seeking to reduce their risk.

INTRODUCTION

Physical activity is crucial for human health and lack thereof is the third most important cause of preventable deaths today.[1] Physical activity as a concept does not only include exercise, but is a measure of how active, or inactive, a person is, and therefore includes all intensities.[2] Several studies, both in healthy individuals and patients with chronic inflammatory diseases, have shown that physical activity results in a reduction in inflammatory markers, highlighting that it influences several biological pathways (reviewed by Beavers *et al*).[3]

For a long time, physical activity was perceived as potentially harmful for patients with rheumatoid arthritis (RA). However, intervention trials have shown during the past decade that physical activity is both well tolerated and improves muscle function in established RA.[4 5] The effect of physical activity before disease onset has, however, not been evaluated before. The aim of this study was to investigate whether leisure time physical activity before disease onset impacts the clinical presentation of RA.

METHODS

Study population

The participants in this study were the patients with newly diagnosed RA, included in the Swedish EIRA study; a population-based case–control study, which has been described elsewhere.[6] From year 2006, questions regarding physical activity 5 years before baseline (ie, at diagnosis) were included in the questionnaire and patients recruited from this year could thus be included in the present study (N=818). Information on disease activity and other clinical features was obtained from the Swedish Rheumatology Quality (SRQ) register, as previously described.[7]

Definition of exposure

Leisure time physical activity 5 years before the diagnosis was assessed by questionnaire; for definitions and examples given in the questionnaire, see table 1. This specific question has been validated in a Swedish population.[8] The four categories of physical activity were also combined to a binary measure, comparing *regular* physical activity with *no regular* physical activity.

Outcome measures

Four clinical measures were used as outcome measures; the 28-joint disease activity score (DAS28), physician assessment of disease activity in five categories (no, low, moderate, high, maximal), health assessment questionnaire (HAQ) and pain on a visual-analogue scale (VAS-pain). We also separately analysed each of the components in the DAS28 score and further combined the objective measures of the DAS28 score; C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and 28-swollen joint count into one group, and the subjective measures; 28-tender joint count and patient global assessment, into one group.

Statistical analysis

We used logistic regression to calculate the odds of scoring above median for each of the outcome measures; complete-case analysis was used. First, we calculated the OR for each of the four categories of physical activity independently (compared with the inactive group), adjusting for sex, period of diagnosis and age at diagnosis (p value for trend was generated by including level of physical activity as a continuous variable). We then compared

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Table 1 Describing the alternative answers to the question "Which of the following alternatives fits your physical activity 5 years ago the best?", which was used to assess exposure in this study

Level	Label	Definition	Examples
1	Sedentary	<2 h PA/week	Mostly reading, TV or other sedentary activates
2	Moderate exercise	≥2 h PA/week	Walking, bicycling, heavy household chores, regular gardening, fishing, table tennis, bowling
3	Regular, moderate exercise	Exercise 1–2 times/week, at least 30 min	Running, swimming, tennis, badminton.
4	Regular exercise and workout	Exercise 3 times/ week, at least 30 min	Running, swimming, badminton, aerobics

regular physical activity with no regular physical activity, where we additionally adjusted for smoking at diagnosis (never/past/current cigarette smokers), body mass index at diagnosis (<25, 25–30 >30 kg/m^2), alcohol intake the last year before diagnosis (five levels), socioeconomic status (highest attained level of education, three levels), vegetable intake the last year before diagnosis (in quartiles) and physically demanding work 5 years before diagnosis (four levels). Effect modifiers were investigated by including interaction terms in the model.

All analyses were carried out using SAS Statistical Package V.9.3. All participants have given informed consent, and the Ethical Review Board at Karolinska Institutet, Stockholm, Sweden, approved the study.

RESULTS

Our final study population consisted of 617 RA patients, after excluding patients not reported to the SRQ register at baseline (diagnostic visit) (N=170), patients who lacked information on physical activity (N=7) and patients who, despite being reported to the register, lacked information on all outcomes measures (N=24). For the 617 included patients, the median symptom duration at diagnosis was 171 days and >90% of the patients had their first symptoms less than a year before diagnosis. For baseline characteristics, see table 2.

Table 3, panel A, displays the effect of each level of physical activity 5 years before RA diagnosis on the OR of having disease measures above median levels at diagnosis. We see a statistically significant trend of lower odds for patients with higher levels of physical activity for all measures (p for trend <0.01 for DAS28, VAS-pain and HAQ, p=0.02 for physician assessment), that is, the higher the level of physical activity, the lower the likelihood of having disease measures above median. For patients classifying their physical activity as 'regular physical activity/workout' (the highest level), the odds of having DAS28, physician assessment, VAS-pain and HAQ above median was significantly reduced by 42–59% compared with inactive patients.

We then compared patients reporting *regular* physical activity with those reporting *no regular* physical activity and found that the former had a 42% reduced odds of having DAS28 above median (OR=0.58 (95% CI 0.42 to 0.81)); table 3, panel B). This was not affected by additional adjustments (OR=0.57 (95% CI 0.39 to 0–82)). Statistically significant effects of a similar magnitude were found for VAS-pain and physician assessment but not for HAQ. In these models, adjusted for sex, period and age, we also investigated potential effect measure modifiers; the effect of physical activity did not differ by anticyclic citrullinated peptide antibodies (anti-CCP) status, sex,

Table 2 Baseline characteristics of RA patients included in the study (N=617)

	N	Per cent
Sex		
Female	447	72
Male	170	28
Age at diagnosis		
<40	107	17
40–50	99	16
50–60	167	27
60–70	244	40
Anti-CCP antibodies*		
Present	399	66
Absent	204	34
Rheumatoid factor*		
Present	397	66
Absent	207	34
Physical activity 5 years before diagnosis		
Inactive	48	8
Some physical activity	281	46
Some regular physical activity	165	27
Regular physical activity/workout	123	20
Smoking habits		
Never	194	31
Past smoker	212	34
Current smoker	147	24
Irregular/other smoker	64	10
Socioeconomic status*		
High	152	25
Medium	316	51
Low	148	24
BMI*		
Normal weight: BMI <25	305	50
Overweight: BMI 25–30	209	34
Obese: BMI >30	101	16
Physically demanding work		
Not working	134	22
Not active	117	19
Somewhat active	167	27
Very active	199	32
Physician assessment on disease activity*		
0=no	5	1
1=low	79	13
2=moderate	316	52
3=high	202	33
4=maximal	10	2

	Median	IQR
Disease activity (DAS28)	5.24	4.53–6.15
Activity limitation (HAQ)*	1.00	0.63–1.50
Pain (VAS)*	56	38–73

*14 patients had missing anti-CCP status, 13 patients had missing rheumatoid factor, 1 patient had missing status at socioeconomic status, 2 patients had missing status for BMI, 15 patients had missing HAQ score, 2 patients had missing pain measurement and 5 patients had missing physician assessment.
anti-CCP, anti-cyclic citrullinated peptide antibodies; BMI, body mass index; DAS28, 28-joint disease activity score; HAQ, health assessment questionnaire; RA, rheumatoid arthritis; VAS, visual analogue scale.

Table 3 Logistic regression calculating the odds of having outcome measure (DAS28, physician assessment (0–4), pain and HAQ, respectively) above median

Panel A	DAS28		Physician assessment		VAS-pain		HAQ	
Physical activity at leisure time	**OR***	**95% CI**	**OR***	**95% CI**	**OR***	**95% CI**	**OR***	**95% CI**
Inactive	1.00	Ref.	1.00	Ref.	1.00	Ref.	1.00	Ref.
Some physical activity	0.84	0.30 to 1.59	0.92	0.49 to 1.74	0.90	0.48 to 1.68	1.04	0.55 to 1.98
Some regular physical activity	0.58	0.30 to 1.12	0.66	0.33 to 1.30	0.60	0.31 to 1.16	0.98	0.50 to 1.92
Regular physical activity / work-out	**0.41**	**0.20 to 0.82**	0.58	0.28 to 1.19	0.52	0.26 to 1.04	**0.49**	**0.24 to 0.99**
p Value for trend	**<0.01**		**0.02**		**<0.01**		**<0.01**	

Panel B	Physical activity at leisure time	Events (N)	OR*	95% CI	OR†	95% CI
DAS28 ≥5.24	No regular physical activity	189	1.00	Ref.	1.00	Ref.
	Regular physical activity	122	**0.58**	**0.42 to 0.81**	**0.57**	**0.39–0.82**
Physician assessment >2	No regular physical activity	130	1.00	Ref.	1.00	Ref.
	Regular physical activity	82	**0.67**	**0.47 to 0.95**	**0.64**	**0.43 to 0.95**
VAS-pain >56	No regular physical activity	181	1.00	Ref.	1.00	Ref.
	Regular physical activity	127	**0.62**	**0.45 to 0.86**	**0.67**	**0.46 to 0.97**
HAQ ≥1	No regular physical activity	194	1.00	Ref.	1.00	Ref.
	Regular physical activity	142	0.71	0.51 to 1.00	0.85	0.58 to 1.23

First, the effect of each category of physical activity is shown, and then the exposure is dichotomised; comparing the effect of *regular* physical activity with *no regular* physical activity.
*Adjusted for sex, age at diagnosis (<40, 40–50, 50–60, 60–65, 65–70 years of age) and period of diagnosis (2006–2008, 2009–2010).
†Additionally adjusted for smoking habits at diagnosis (never/past/current cigarette smokers), body mass index at diagnosis (<25, 25–30, >30 kg/m^2), alcohol intake at diagnosis (five levels), socioeconomic status (assessed as highest attained level of education, three levels), vegetable intake the last year before diagnosis (in quartiles) and physically demanding work 5 years before diagnosis (four levels).
DAS28, disease activity score 28 joints; HAQ, health assessment questionnaire; VAS, visual-analogue scale.

body mass index (BMI), socioeconomic status or physically demanding work. As an additional analysis, we investigated the odds of having high disease activity, defined as DAS28 >5.1; this cut-off was similar to the median DAS28 in this population (5.24) and lead to a similar result (OR for regular physical activity=0.71 (95%CI 0.49 to 1.02)) (data not shown in table).

To investigate whether the association between physical activity and DAS28 was driven specifically by any of the measures that constitute the DAS28 score, we separately calculated the p value for each of the components and found significant associations between physical activity and ESR, CRP and patient global assessment (data not shown in table). Further, regular physical activity 5 years before diagnosis was associated with 40% decrease in odds of having all objective measures above median (OR=0.60 (95% CI 0.40 to 0.88)), and 35% decreased odds of having both subjective measures above median (OR=0.65 (95% CI 0.45 to 0.95)).

DISCUSSION

In summary, this first study of physical activity before disease onset and the clinical presentation of RA shows that regular physical activity is associated with a milder disease at diagnosis. The association was consistent across subgroups of this heterogenic syndrome and remained after adjustment for potential confounders. The beneficial effect of regular physical activity was seen for both the objective and the subjective components of the DAS28 score.

No previous studies have evaluated the influence of physical activity on the clinical presentation of RA. However, disease activity has commonly been included as an outcome in clinical trials of physical activity in established RA patients. In a review by Stenström and Minor,[3] six studies reported an improvement and eight found no change in disease activity after physical activity intervention, while only a small minority of the studies included and reported improvements in VAS-pain or HAQ. The results of the present study implicate that only the highest level of physical activity is sufficient to have a beneficial effect on HAQ; in general, the knowledge of the levels and patterns of physical activity needed for beneficial effects needs to be further elucidated.

We found that CRP, ESR and patient global assessment were significantly affected by physical activity, which corresponds to research on healthy individuals, in whom physical activity resulted in decreased CRP and ESR.[3 9 10] Since the odds of both the objective and the subjective groups of DAS28 components were found to be significantly decreased by regular physical activity, the effect does not seem confined to any specific component of DAS28.

Regularly physically active people are a selected subpopulation, although perhaps less so in Sweden, where 50% of the population is estimated to fulfil the recommendations of at least 30 min of physical activity every day.[11 12] Physical activity has been shown to correlate with high socioeconomic status, younger age, non-smoking, normal BMI and high vegetable intake.[9 13] We had the possibility to adjust for all these factors, but the estimates were not affected.

Physical activity is likely acting on the human body by multiple different mechanisms, several of them connected to chronic inflammation and its markers, as reviewed in Perandini *et al*.[14] An example of the potency of physical activity was shown in a gene-expression analysis of patients suffering from another chronic inflammatory disease, myositis, where even a short period of just 7 weeks had profound effects on the gene-expression in the inflammatory pathways.[15] Further, Barres *et al* showed that a single episode of exercise gave rise to transient hypomethylation, and subsequent upregulation, of genes in skeletal muscle.[16] In the present study, physical activity 5 years before diagnosis is assumed to indicate a physically active lifestyle as the level of physical activity in adults has been shown to be relatively constant.[17]

Strengths of this study include its population-based setting and the extensive information available, which made adjustments for a multitude of potential confounders possible. In observational

studies, *reverse causality* can never be entirely excluded. It might be particularly likely when investigating an association such as that between physical activity and RA, where it is conceivable that early RA symptoms would lead to decreased physical activity. Reassuringly, we were able to measure physical activity 5 years before diagnosis, which was, on average, 4.45 years before symptom onset. Previous studies have shown that 25% of RA patients have rheumatoid factor and/or anti-CCP antibodies present 5 years before diagnosis; we however find it unlikely that the presence of autoantibodies without symptoms would affect the physical activity.[18] Finally, our exposure is self-reported, which is likely to lead to some misclassification, presumably non-differential since both exposed and unexposed are RA patients, this would in turn lead to bias towards the null and thus underestimate the true association.

In conclusion, our findings demonstrates that RA patients who are physically active before clinical disease onset present with a milder disease, both in terms of inflammation, pain and function. This adds to the growing evidence of general beneficial health effects of physical activity and is an important message for individuals at increased risk of RA, as well as for health professionals, similarly to the recent findings regarding smoking and overweight.[19]

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Competing interests None.

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