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# Intérêt de l'activité physique aérobie et du renforcement musculaire dans la polyarthrite rhumatoïde : analyses systématiques de la littérature et méta-analyses d'essais randomisés contrôlés

Athan Baillet

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**Université de Grenoble**

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**MEMOIRE**

pour l'obtention du Diplôme de Docteur en Médecine

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Présenté et soutenu le 1<sup>er</sup> septembre 2011

par

**BAILLET Athan**

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**Intérêt de l'activité physique aérobie et du renforcement musculaire dans la polyarthrite rhumatoïde : analyses systématiques de la littérature et méta-analyses d'essais randomisés contrôlés**

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## **ABBREVIATIONS**

CLEAR-NPT = A Checklist to Evaluate a Non-Pharmacological Trial

DAS 28 = Disease Activity Score based on 28 joints

ES = Effect Size

EVA = Echelle Visuelle Analogique

HAQ = Health Assessment Questionnaire

IGF-1 = Insulin-like Growth Factor 1

IL-6 = Interleukine 6

OR = Odds Ratio

PR = Polyarthrite Rhumatoïde

RR = Risque Relatif

SDD = Smallest Detectable Change

SMD = Standardized Mean Difference

WMD = Weighted Mean Difference

MCID = Minimally Clinically Important Difference

## INTRODUCTION

La polyarthrite rhumatoïde (PR) est une pathologie multifactorielle, avec un terrain génétique [1] particulier impliquant des facteurs environnementaux tels que le tabac [2, 3] et la flore microbienne [4], qui touche 0,4% de la population caucasienne [5]. Les traitements immuno-modulateurs et les thérapeutiques ciblées ont largement contribué à l'amélioration de la prise en charge des patients, permettant de diminuer l'activité de la maladie [6], d'améliorer le handicap [7], la qualité de vie [6] et l'évolution structurale [6, 8-10], mais au prix des effets indésirables [11] parfois sévères [12, 13] et avec un coût important sur l'économie de santé [14, 15].

L'activité physique, définie comme un « mouvement du corps produit par un ou des groupes musculaires à l'origine d'une dépense énergétique » [16] regroupe à la fois l'exercice physique de la vie quotidienne (déplacements, travail, tâches ménagères...), l'activité physique de loisirs, et la pratique sportive qui est un "sous-ensemble spécialisé et organisé de l'activité physique". On distingue généralement trois types d'activités sportives : l'exercice aérobie, le renforcement musculaire et les assouplissements. Pendant longtemps, l'exercice physique était suspecté d'augmenter l'activité des rhumatismes inflammatoires [17] et de provoquer des lésions structurales en élevant la pression intra-articulaire [18] responsable d'une baisse de la perfusion dans le pannus [19]. Il s'ensuivrait des phénomènes d'ischémie-reperfusion localisés à l'origine d'une protéolyse matricielle [20]. Cette destruction articulaire est, au moins en partie, secondaire à une production accrue de dérivés radicalaire de l'oxygène [21-23]. Il faut attendre les années 90 pour que des études néerlandaises et scandinaves suggèrent une relative innocuité de la pratique de l'activité physique dans la PR stable [24-30].

Dans une étude récente nous avons montré qu'un programme d'exercices dynamiques améliore la fonction des patients atteints de PR (**Annexe 1**, [31]), allant à l'encontre des résultats d'études publiées auparavant [30, 32]. Les articles de revue précédents [33, 34],

n'ayant pas clairement permis de savoir si l'exercice physique était bénéfique pour les patients atteints de PR, nous avons conduit une analyse systématique de la littérature afin de savoir si l'exercice aérobie d'une part et le renforcement musculaire d'autre part amélioreraient les principaux critères d'évaluation de la PR. Nous avons effectué une méta-analyse afin d'aboutir à des conclusions chiffrées, de dégager la pertinence clinique de l'efficacité de l'intervention physique et de chercher un facteur d'hétérogénéité expliquant les différences entre les études.

Dans une première partie, nous nous intéresserons à l'impact de l'exercice aérobie dans la PR. Cette étude a été présentée en communication orale au congrès européen de rhumatologie (European League Against Rheumatism) en 2009 à Copenhague et publiée dans la revue *Arthritis Care and Research* en 2010 [35]. Dans une deuxième partie, nous étudierons l'intérêt du renforcement musculaire dans la PR. Ce travail a été soumis en mars 2011 pour publication au journal *Rheumatology* [36].

## **PARTIE I**

# **Intérêt de l'activité physique aérobie dans la polyarthrite rhumatoïde : Analyse systématique de la littérature et méta-analyse d'essais randomisés contrôlés**



## **PARTIE I : SYNOPSIS DU PREMIER ARTICLE**

### Introduction :

Il est déjà établi que la force de préhension et la capacité aérobie sont améliorées chez les patients atteints de PR participant aux programmes de rééducation dynamique. L'objectif de cette première étude était de déterminer l'effet de l'activité physique aérobie sur la fonction, la qualité de vie, la douleur, l'activité de la maladie et la progression radiologique des patients atteints de PR.

### Patients et Méthodes :

Tous les essais randomisés contrôlés évaluant l'activité physique ont été systématiquement recherchés dans les bases de données Medline, Cochrane et EMBase en juillet 2009. Le groupe intervention devait bénéficier d'exercices aérobies alors que le groupe contrôle était soumis à des exercices isométriques ou à une absence d'exercice. La variation des données suivantes a été étudiée : la fonction sur le Health Assessment Questionnaire (HAQ), la qualité de vie, l'échelle visuelle analogique douleur (EVA), l'activité de la maladie sur le Disease Activity Score (DAS28), le compte articulaire et l'indice radiologique de Larsen. La tolérance était évaluée par le nombre de patient qui achevaient l'étude et le nombre d'effets indésirables. La qualité méthodologique de chaque étude était analysée sur le score de Jadad (0-5) et CLEAR-NPT (A Checklist to Evaluate a Non-Pharmacological Trial ; 0-14).

Une méta-analyse par le modèle de l'inverse de la variance a été effectuée. Les résultats ont été exprimés au moyen de la différence des moyennes standardisées (Standardized mean difference SMD) pour les variables quantitatives et en odds ratio (OR) pour les variables qualitatives ainsi que leurs intervalles de confiance à 95% (IC95%). Les SMD et les OR ont été agrégés en comparant le groupe actif au groupe contrôle. Une SMD>0.20 est considérée comme modeste et >0.40 comme modérée. Une analyse de sous-groupe a été conduite pour identifier un facteur d'hétérogénéité entre les études. Un biais de publication a été recherché par analyse graphique et par les tests statistiques de Begg et Egger.

### Résultats :

14 essais randomisés contrôlés ont été analysés (soit 1040 patients). Le score moyen de Jadad était  $2,4 \pm 0,4$  alors que seulement 2 articles validaient au moins 7 items du CLEAR-NPT. L'exercice aérobie améliorait la fonction évaluée par le HAQ (SMD = 0,24, IC95% [0,10, 0,38],  $p = 0,0009$ ), la qualité de vie (SMD = 0,39, IC95% [0,23, 0,56],  $p < 0,0001$ ), l'EVA douleur (SMD = 0,31, IC95% [0,06, 0,55],  $p = 0,02$ ). L'exercice physique n'avait pas d'effet délétère sur l'activité de la maladie mesurée par le DAS 28 (SMD = -0,16 [-0,47, 0,15],  $p = 0,34$ ), le compte articulaire (SMD = 0,14, IC95% [-0,05, 0,33],  $p = 0,14$ ) et semble même avoir un effet positif sur le score radiologique de Larsen (SMD = 0,36, IC95% [0,16, 0,56],  $p = 0,0005$ ). Le groupe qui bénéficiait d'exercices aérobies comptait le même nombre de patients achevant l'étude que le groupe contrôle (respectivement 86,8% et 87,3% ; OR = 0,80, IC95% [0,56, 1,16],  $p = 0,24$ ). De même, il n'existait pas de différence de tolérance entre le groupe intervention et le groupe contrôle (respectivement 47 (9,2%) et 34 (6,4%) évènements indésirables ; OR=1,67, IC95% [0,36, 7,69],  $p = 0,51$ ). La supervision des exercices améliorait l'effet positif sur la qualité de vie. On notait une hétérogénéité des résultats en fonction de la qualité méthodologique des études. Un biais de publication pour l'effet sur le HAQ était possible.

### Discussion :

Nous avons pu démontrer un impact favorable de l'exercice aérobie sur le HAQ, la qualité de vie, l'évolution structurale et la douleur sans effet péjoratif sur le compte articulaire ou l'activité de la maladie. On notait une certaine hétérogénéité entre ces études dont la qualité méthodologique était moyenne.

### Conclusion :

Ces résultats plaident pour une augmentation de prescription des activités physiques aérobies pour les patients atteints de PR.

# Efficacy of Cardiorespiratory Aerobic Exercise in Rheumatoid Arthritis: Meta-Analysis of Randomized Controlled Trials

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**Objective.** Several lines of evidence have emphasized an improvement in aerobic capacity and muscle strength after physical exercise programs in rheumatoid arthritis (RA) patients. Our objective was to evaluate the efficacy of aerobic exercises in RA on quality of life, function, and clinical and radiologic outcomes by a systematic literature review and a meta-analysis.

**Methods.** A systematic literature search was performed in the Medline, EMBase, and Cochrane databases up to July 2009 and in the abstracts presented at rheumatology scientific meetings during the last 5 years. Randomized controlled trials (RCTs) comparing aerobic exercises with non-aerobic interventions in RA patients were included. Outcomes studied were postintervention quality of life, function assessed by the Health Assessment Questionnaire (HAQ), a pain visual analog scale (VAS), joint count, the Disease Activity Score in 28 joints (DAS28), and radiologic damage. Efficacy was assessed by standardized mean differences (SMDs; difference between groups of mean outcome variation from baseline/SD at baseline) of aerobic exercises versus non-aerobic rehabilitation. Heterogeneity was tested. SMDs were pooled by a meta-analysis using the inverse of variance model.

**Results.** Fourteen RCTs, including 1,040 patients, met the inclusion criteria. Exercise improved the postintervention quality of life (SMD 0.39,  $P < 0.0001$ ), HAQ score (SMD 0.24,  $P = 0.0009$ ), and pain VAS (SMD 0.31,  $P = 0.02$ ). Exercise in this RA population appeared safe, since global compliance, DAS28, and joint count were similar in both groups.

**Conclusion.** Cardiorespiratory aerobic conditioning in stable RA appears to be safe and improves some of the most important outcome measures. However, the degree of the effect of aerobic exercise on the abovementioned parameters is small.

## INTRODUCTION

Impairment in range of motion, muscle strength, endurance, and aerobic fitness results in serious loss of function,

work disability, dependency, impaired social or family function, and reduced quality of life in rheumatoid arthritis (RA) patients (1). Even if pharmacologic interventions have largely improved RA management over the past decade, physical therapy remains an important part of treatment. Previously, the exercise therapy in RA aimed only at maintaining joint mobility and muscle strength. Because exercises were thought to provoke joint damage by enhancing disease activity (2), patients with inflammatory arthritis, especially RA, were discouraged from performing weight-bearing exercises. In a previous randomized controlled trial (RCT), we showed that an exercise program had a greater impact on both disability assessed by the Health Assessment Questionnaire (HAQ) and quality of life than conventional joint rehabilitation (3), contrasting with most of the previous similar studies that failed to detect any statistical difference on the HAQ (4,5) or quality of life (6). Several trials showed that exercises were safe in RA rehabilitation and effectively improved aerobic fitness (3,5,7,8). Previous systematic literature reviews of the efficacy of physical exercises in RA patients confirmed these results (9,10). Given the limited number of studies, review-

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ers decided not to pool data and were therefore unable to draw numerical conclusions concerning the efficacy of exercise programs on other important outcome measures in RA. During the past few years, several trials have been carried out to examine the effect of exercises in RA, but results with respect to pain, disease activity, functional ability, quality of life, and structural damage are still unclear. We therefore carried out this systematic literature review in order to determine whether aerobic exercises effectively improve the abovementioned parameters in RA.

## MATERIALS AND METHODS

**Type of intervention.** A cardiorespiratory aerobic exercise is an exercise that improves  $\text{VO}_2$  and is usually performed at 50–80% of the maximal heart rate ( $220 - \text{age}$ ). The American College of Sports Medicine defined a dynamic exercise program as aerobic exercises performed at between 60% and 80% of the maximal heart rate at least twice a week for 6 weeks (11). Strengthening exercises and aerobic exercises without training intensity (i.e., maximal heart rate) monitoring were not examined in this systematic review.

Non-aerobic rehabilitation was defined by the following terms: “static,” “range of motion,” “isometric,” “seated immersion,” “relaxation,” “stretching,” “no attention,” or “usual care.” As a consequence, trials with aerobic exercises in the control group were not considered.

**Search strategy.** An extensive search of PubMed, EMBase, and the Cochrane Central Register of RCTs (until July 28, 2009) was made by two reviewers (AB and L-AB). The following keywords were used for database screening: (“Arthritis, Rheumatoid” [medical subject headings (MeSH)]) AND (“Exercise Therapy” [MeSH] OR “Activities of Daily Living” [MeSH] OR “Physical Education and Training” [MeSH]). The only limit of the search was “clinical trial.” A hand search of references from relevant articles, from review articles, and from abstracts presented at the Annual Scientific Meetings of the American College of Rheumatology (ACR), the Annual Congress of the European League Against Rheumatism, and the Scientific Meetings of the French Society of Rheumatology published in the past 5 years completed the search. A search on the ClinicalTrials.gov Web site was also performed to identify randomized studies that were not yet published.

**Selection.** Inclusion criteria were an RCT evaluating cardiorespiratory aerobic exercises performed at 50–90% of the maximal heart rate in comparison with non-aerobic rehabilitation in adult patients with RA as defined by the ACR (formerly the American Rheumatism Association) criteria (12,13). Exclusion criteria consisted of postsurgery rehabilitation and articles written in a language other than English, French, or German.

**Quality assessment.** A single author (AB) assessed the methodologic quality of each study included in the meta-

analysis on both the Jadad scale (14) and the Checklist to Evaluate A Report of a Non-Pharmacological Trial (CLEAR-NPT) (15), ranging from 0–5 and 0–14, respectively, where a high score indicates high quality.

**Data extraction.** One investigator (AB) selected the articles and collected the data using a predetermined form, including study design (randomization procedure, blinding, followup period, and intent-to-treat analysis), patient characteristics (number, age, sex, disease duration, functional status, treatment, rate of rheumatoid factor [RF]-positive patients, and proportion of completers), and intervention parameters (duration of an exercise session, overall duration of the intervention, exercise type, frequency, and intensity, i.e., maximal heart rate).

**Outcomes.** We used the Cochrane Musculoskeletal Group recommendation to select outcome measures (16). We reported tender joint count, swollen joint count, pain, and disability. We also reported data concerning withdrawals (i.e., the number of completers) and adverse effects in order to assess exercise safety. The following outcomes (the references of which are available in Supplementary Table 1, available in the online version of this article at <http://www3.interscience.wiley.com/journal/77005015/home>) were extracted from the publications: 1) quality of life, evaluated on the Nottingham Health Profile (NHP), the Rheumatoid Arthritis Quality of Life (RAQoL) questionnaire, the physical component of the 36-item Short Form health survey (SF-36), the Arthritis Impact Measurement Scales Health Status Questionnaire (AIMS), and the McMaster Toronto Arthritis Patient Preference Disability Questionnaire (MACTAR); 2) function, assessed by the HAQ; 3) the Disease Activity Score in 28 joints (DAS28); the DAS4 was converted into the DAS28 as follow:  $\text{DAS28} = (1.072 \times \text{DAS4}) + 0.938$ ; 4) joint count (number of swollen joints, number of tender joints, and Ritchie Articular Index); 5) pain on a visual analog scale (VAS); 6) radiologic evaluation by Larsen’s method; and 7) exercise tolerance, evaluated both by exercise compliance (i.e., the number of completers) and by exercise safety. For the latter parameter, we reported adverse effects such as steroid injection due to local disease flare, cardiovascular events, and joint/muscle soreness.

Quality of life and joint count evaluations were expressed as a percentage of the maximum possible score for the method used. Standardized data abstraction concerned means or medians and measures of dispersion. Since the measure of dispersion for change was not always available, a conservative estimate was taken from baseline data and converted into an SD. When median values were given instead of mean values, the median was analyzed as a mean. Data were collected at several end points: baseline, 1 month  $\pm$  2 weeks, 3 months  $\pm$  4 weeks, 6 months  $\pm$  2 months, 1 year, and 2 years or more. When a trial was reported in several publications, the more informative publication was included in the meta-analysis. When studies reported more than 2 subgroups, we included only the first intervention group described in this study and its corresponding control group.

**Statistical analysis.** Heterogeneity was tested using Cochran's test.  $I^2$  values  $>50\%$  were defined to indicate significant heterogeneity. The efficacy of intervention versus non-aerobic rehabilitation was assessed in each study by the calculation of the standardized mean difference (SMD; difference between both groups of mean outcome variation from baseline/SD at baseline) and 95% confidence interval (95% CI). Individual SMDs were pooled using the method of the inverse of variance. Intervention safety was assessed by the odds ratio (OR) and 95% CI. The results of individual trials were pooled by meta-analysis using the Mantel-Haenszel method. In case of heterogeneity, a random-effects model was used (17). Otherwise, a fixed-effects model was applied. SMDs between 0.2 and 0.5 indicated a small effect, between 0.5 and 0.8 indicated a medium effect, and  $>0.8$  indicated a large effect. To relate the efficacy in SMD units to a more familiar outcome, we transformed the SMD into the difference in mean outcome scores (experimental versus control) on that scale (18). Meta-analyses were done with Review Manager 5 (Cochrane), and additional statistics were developed with StatsDirect software (StatsDirect).

**Sensitivity analysis and heterogeneity assessment.** A sensitivity analysis was conducted to evaluate the robustness of the meta-analysis by assessing the influence of an individual study on the overall SMD. We therefore examined the effect of removing each study individually from the meta-analysis. To explore heterogeneity, we combined studies into 2 or 3 subgroups according to the trial design (published before or after 2000, Jadad scale score  $<3$  or  $\geq 3$ ), the disease characteristics (mean disease duration  $<5$  years or  $\geq 5$  years, functional status class I–II or including class III), and the intervention parameters (supervised or home based; overall duration of the intervention  $<3$ , 3, or  $>3$  months; exercise frequency  $<3$  or  $\geq 3$  times/week; duration of an exercise session  $<30$ , 30–60, or  $>60$  minutes). Heterogeneity between the subgroups was tested using a chi-square test (19).

Publication bias was assessed using funnel plot analysis, Begg's test, and Egger's test.

## RESULTS

**Trial flow.** A total of 513 abstracts were identified by database searching and 6 articles by hand searching. Of these, 140 duplicates were removed and 298 abstracts were excluded because of no physical exercise ( $n = 95$ ), no RA patients ( $n = 171$ ), age  $<18$  years ( $n = 13$ ), postsurgery rehabilitation ( $n = 9$ ), no RCT ( $n = 9$ ), and language ( $n = 1$ ). Eighty-one full-text reports were analyzed and 67 articles were excluded because of previous publication ( $n = 7$ ), other joint disease ( $n = 18$ ), no RCT or aerobic exercise in the control group ( $n = 14$ ), no aerobic exercise in the intervention group ( $n = 11$ ), training intensity not provided ( $n = 5$ ), and no extractable data ( $n = 12$ ). Fourteen articles were finally entered in the analysis.

**Study characteristics.** Study characteristics are shown in Table 1. The mean  $\pm$  SD Jadad scale score was  $2.4 \pm 0.6$ .

Seven trials displayed a Jadad scale score  $<3$  and only 2 trials validated 7 CLEAR-NPT items. Among the 14 trials with cardiorespiratory aerobic exercise conditioning, the intervention fulfilled the dynamic exercise program criteria in 5 studies (5,8,20–22). The control group underwent range of motion exercises in 3 studies (5,22,23), non-aerobic exercises in 1 study (24), education programs in 2 studies (3,25), and usual care in 8 studies (8,20,21,26–30).

**Patients' characteristics.** The meta-analysis included 1,040 patients (510 patients in the intervention group and 530 in the control group). Both groups were similar in terms of age, disease duration, sex ratio, proportion of completers, rate of RF-positive patients, and pharmaceutical treatments (see Supplementary Table 2, available in the online version of this article at <http://www3.interscience.wiley.com/journal/77005015/home>). Mean age and disease duration in the studies ranged from 44–68 years and 1–16 years, respectively (in the 13 trials reporting these parameters). For the 11 studies for which sex was reported, 46.7–100% were women. The rate of RF-positive patients ranged from 59–93.3% in the 5 studies assessing this parameter.

**Meta-analysis.** Data on quality of life were available for 5 studies, including 298 patients in the intervention group and 288 in the control group. This outcome was measured by the AIMS (26), the NHP (3), the RAQoL (25), the SF-36 (24), or the MACTAR (20) (see Supplementary Table 3, available in the online version of this article at <http://www3.interscience.wiley.com/journal/77005015/home>). A small beneficial effect of aerobic intervention on the quality of life of RA patients was shown (SMD 0.39 [95% CI 0.23, 0.56],  $P < 0.0001$ ) (Figure 1). Heterogeneity was not statistically significant in this subset of studies ( $I^2 = 45\%$ ).

Nine studies evaluated the impact of aerobic exercises on the HAQ, comprising a total of 387 patients in the intervention group and 384 patients in the control group (Figure 2). Exercises provided a small positive effect on the HAQ (SMD 0.24 [95% CI 0.10, 0.38],  $P = 0.0009$ ;  $I^2 = 29\%$ ).

Data on the pain VAS were available in 6 studies (138 patients in the intervention group and 123 in the control group). The overall SMD for pain measured by the VAS was 0.31 (95% CI 0.06, 0.55;  $P = 0.02$ ,  $I^2 = 30\%$ ) (Figure 3).

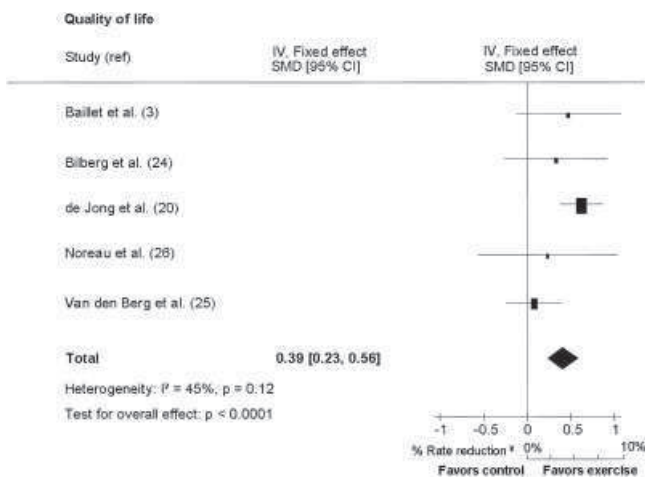
Nine studies, including 228 patients in the intervention group and 209 patients in the control group, evaluated joint count. The Ritchie Articular Index was reported in 2 trials (5,23), swollen joint count in 2 studies (21,27), tender joint count in 2 studies (26,28), and both swollen and tender joint counts in 3 studies (8,22,29) (see Supplementary Table 3, available in the online version of this article at <http://www3.interscience.wiley.com/journal/77005015/home>). Intervention tended to provide a positive effect on this outcome, although the difference did not reach the statistical significance (SMD 0.14 [95% CI  $-0.05$ , 0.33],  $P = 0.14$ ;  $I^2 = 0\%$ ) (Figure 4).

Only 3 studies evaluating 376 RA patients for radiologic damage as assessed by radiologic findings were available

Table 1. Trial characteristics\*

Author, year (ref.)	Country	Jadad scale score	Function status	Intervention group							Control group	
				Patients, no.	Exercise type	Max HR, %	Frequency, per week	Duration, minutes	Length, weeks	Attendance, %	Patients, no.	Comparator
Bilberg et al, 2005 (24)	Sweden	3	Steinbrocker I-III	22	Supervised cardiorespiratory aerobic conditioning	70	2	45	12	78	27	Non-aerobic exercises
Van den Berg et al, 2006 (25)	The Netherlands	3	nr	82	Home-based cardiorespiratory aerobic conditioning	60-80	5	10-30	52	34	78	Education
De Jong et al, 2003 (20)	The Netherlands	3	ACR I-III	150	Supervised DEP	70-90	2	75	104	74†	150	Usual care
Westby et al, 2000 (8)	Canada	2	ACR I-II	14	Home-based DEP	60-75	3	45-60	52	71	16	Usual care
Van den Ende et al, 2000 (22)	The Netherlands	3	nr	34	Supervised DEP	60	3	15	~4	nr	30	ROM exercises
Melikoglu et al, 2006 (23)	Turkey	2	ACR I-II	20	Supervised cardiorespiratory aerobic conditioning	60	2	20	2	nr	20	ROM exercises
Hansen et al, 1993 (27)	Denmark	2	Steinbrocker I-II	60	Home-based cardiorespiratory aerobic conditioning	70	≥3	<90	104	>50	15	Usual care
Harkcom et al, 1985 (21)	US	2	Steinbrocker II	14	Supervised DEP	70	3	15-35	12	nr	6	Usual care
Van den Ende et al, 1996 (5)	The Netherlands	3	nr	75	Supervised and home-based DEPs	70-85	3	60	12	75	25	ROM exercises
Baillet et al, 2009 (3)	France	3	ACR I-II	25	Supervised cardiorespiratory aerobic conditioning	60-80	5	45	4	100	23	Education
Neuberger et al, 2007 (29)	US	3	nr	173	Supervised and home-based cardiorespiratory aerobic conditioning	60-80	3	60	12	83	75	Usual care
Nordemar et al, 1981 (30)	Sweden	1	ACR I-III	23	Home-based cardiorespiratory aerobic conditioning	70	‡	60	52	nr	23	Usual care
Noreau et al, 1995 (26)	Canada	2	ACR I-II	19	Supervised cardiorespiratory aerobic conditioning	50-70	2	15-30	12	83	10	Usual care
Lyngberg et al, 1994 (28)	Denmark	2	Steinbrocker I-III	12	Supervised cardiorespiratory aerobic conditioning	50-70	2	45	12	nr	12	Usual care

\* Max = maximal; HR = heart rate; nr = not reported/inapplicable; ACR = American College of Rheumatology; DEP = dynamic exercise program; ROM = range of motion.  
 † The median percentage of sessions attended was 74% (interquartile range 27%), 30% of patients had a 50-75% attendance rate, and 49% of patients had a high attendance rate (>75%).  
 ‡ One hour daily (supervised) every second week plus 30 minutes daily (home based), leading to a mean ± SD training time of 339 ± 179 minutes/week.

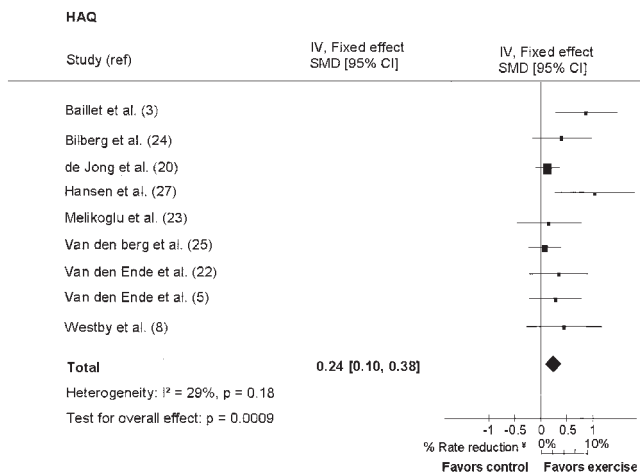


**Figure 1.** Efficacy of cardiorespiratory aerobic exercises on quality of life. ¥ = percentage of rate reduction compared with the control group; SMD = standardized mean difference; 95% CI = 95% confidence interval; IV = method of the inverse of variance.

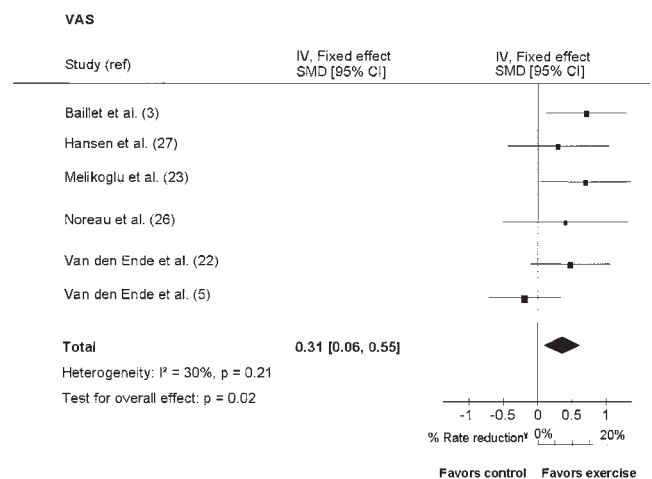
(188 patients in each group). Aerobic exercise training was suspected to have a joint damage sparing effect because the SMD was 0.36 (95% CI 0.16, 0.56;  $P = 0.0005$ ,  $I^2 = 17\%$ ) (see Supplementary Figure 1, available in the online version of this article at <http://www3.interscience.wiley.com/journal/77005015/home>).

Disease activity, evaluated by the DAS28, was recorded in 4 studies (291 patients in the intervention group and 281 patients in the control group). The exercise group did not display a worse DAS28 score (SMD 0.08 [95% CI -0.08, 0.25],  $P = 0.34$ ;  $I^2 = 67\%$ ).

Both groups had similar numbers of completers: 460 (86.8%) of 530 patients in the intervention group versus 445 (87.3%) of 510 patients in the control group (OR 0.80 [95% CI 0.56, 1.16],  $P = 0.24$ ;  $I^2 = 55\%$ ). Forty-seven adverse events were reported in the intervention group and 34 adverse events were reported in the control group. However, the difference was not statistically significant



**Figure 2.** Efficacy of cardiorespiratory aerobic exercises on function, assessed by the Health Assessment Questionnaire (HAQ). ¥ = percentage of rate reduction compared with the control group; SMD = standardized mean difference; 95% CI = 95% confidence interval; IV = method of the inverse of variance.

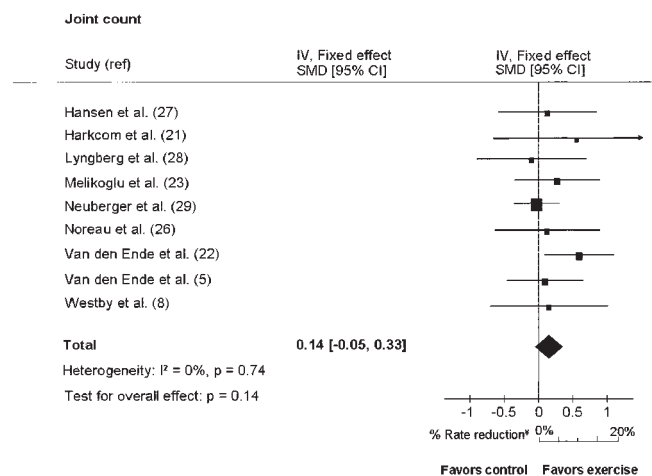


**Figure 3.** Efficacy of cardiorespiratory aerobic exercises on a pain visual analog scale (VAS). ¥ = percentage of rate reduction compared with the control group; SMD = standardized mean difference; 95% CI = 95% confidence interval; IV = method of the inverse of variance.

(OR 1.67 [95% CI 0.36, 7.69],  $P = 0.51$ ;  $I^2 = 73\%$ ). Steroid injection in both groups was similar (OR 0.85 [95% CI 0.42, 1.29],  $P = 0.98$ ;  $I^2 = 0\%$ ). Three cardiovascular events were reported in the 14 trials. One myocardial infarction and one pulmonary embolism occurred in the intervention group. It was not possible to determine in which group the remaining cardiovascular event occurred. A single trial reported joint soreness and a compression fracture in the exercise group.

**Heterogeneity exploration and sensitivity analysis.** No statistical heterogeneity was detected in the outcome measures, except for disease activity on the DAS28.

Aerobic cardiorespiratory conditioning ameliorated the HAQ in patients with class I–II functional status, whereas it barely had any effect in patients with more severe functional status (Table 2). Disease duration influenced quality of life and pain. In early RA (disease duration <5 years)



**Figure 4.** Efficacy of cardiorespiratory aerobic exercises on joint count. ¥ = percentage of rate reduction compared with the control group; SMD = standardized mean difference; 95% CI = 95% confidence interval; IV = method of the inverse of variance.

Table 2. Heterogeneity exploration\*

	Quality of life		HAQ		Joint count		Pain VAS	
	SMD (95% CI)	I <sup>2</sup> , %	SMD (95% CI)	I <sup>2</sup> , %	SMD (95% CI)	I <sup>2</sup> , %	SMD (95% CI)	I <sup>2</sup> , %
Patient parameters								
Functional status								
Class I-II	0.36 (-0.09, 0.82)	0	0.60 (0.27, 0.94)	28	0.21 (-0.14, 0.56)	0	0.34 (0.08, 0.59)	27
Including class III	0.55 (0.34, 0.77)	0	0.16 (-0.05, 0.37)	0	0.11 (-0.69, 0.91)	0	NA	NA
Chi-square test, <i>P</i>	0.47		0.03		0.48		NA	
Disease duration								
<5 years	0.55 (0.34, 0.77)	0	0.22 (0.01, 0.42)	63	NA	NA	0.03 (-0.34, 0.41)	0
≥5 years	0.16 (-0.10, 0.42)	0	0.26 (0.07, -0.46)	15	0.15 (-0.05, 0.34)	0	0.56 (0.32, 0.79)	0
Chi-square test, <i>P</i>	0.02		0.75		NA		0.02	
Exercise parameters								
Frequency								
<3 times/week	0.53 (0.32, 0.73)	0	0.16 (-0.07, 0.26)	0	0.01 (-0.54, 0.56)	0	0.31 (-0.25, 0.87)	0
≥3 times/week	0.12 (-0.12, 0.43)	23	0.26 (0.11, 0.41)	36	0.35 (0.05, 0.66)	0	0.43 (0.21, 0.64)	47
Chi-square test, <i>P</i>	0.03		0.28		0.29		0.71	
Duration of session								
<30 minutes	0.07 (-0.38, 0.24)	NA	0.19 (0.07, 0.46)	61	0.33 (-0.23, 0.88)	0	0.56 (0.04, 1.08)	0
30-60 minutes	0.28 (-0.18, 0.73)	0	0.41 (-0.04, 0.87)	0	0.01 (-0.54, 0.56)	0	NA	NA
>60 minutes	0.57 (0.36, 0.78)	0	0.24 (-0.05, 0.42)	45	0.36 (-0.13, 0.86)	42	0.38 (0.17, 0.60)	73
Chi-square test, <i>P</i>	0.03		0.71		0.56		0.54	
Program duration								
<3 months	0.45 (-0.13, 1.02)	0	0.52 (0.09, 0.95)	62	0.27 (-0.35, 0.89)	0	0.67 (0.24, 1.09)	0
3 months	0.28 (-0.19, 0.74)	NA	0.37 (-0.04, 0.77)	0	0.35 (-0.01, 0.70)	0	0.50 (0.23, 0.77)	0
>3 months	0.40 (0.22, 0.59)	86	0.18 (-0.02, 0.34)	34	0.09 (-0.46, 0.65)	NA	0.04 (-0.46, 0.37)	11
Chi-square test, <i>P</i>	0.86		0.28		0.75		0.04	
Supervision								
Supervised	0.52 (0.32, 0.71)	0	0.25 (0.09, 0.42)	1	0.15 (-0.05, 0.34)	0	0.34 (0.08, 0.59)	27
Home based	0.07 (-0.24, 0.38)	NA	0.20 (-0.08, 0.49)	73	NA	NA	NA	NA
Chi-square test, <i>P</i>	0.02		0.28		NA		NA	
Trial design								
Publication date								
Before 2000	0.28 (-0.19, 0.74)	0	0.46 (0.12, 0.80)	26	0.14 (-0.18, 0.46)	0	0.03 (-0.34, 0.41)	0
After 2000	0.41 (0.23, 0.58)	72	0.19 (0.04, 0.35)	25	0.59 (0.09, 1.09)	0	0.56 (0.32, 0.79)	0
Chi-square test, <i>P</i>	0.60		0.16		0.14		0.02	
Methodology								
Jadad scale score <3	0.28 (-0.19, 0.74)	0	0.46 (0.08, 0.83)	36	0.17 (-0.22, 0.56)	0	0.46 (0.04, 0.88)	0
Jadad scale score ≥3	0.41 (0.23, 0.58)	68	0.20 (0.05, 0.36)	20	0.37 (-0.01, 0.74)	42	0.40 (0.17, 0.62)	22
Chi-square test, <i>P</i>	0.60		0.22		0.47		0.78	

\* The efficacy of aerobic exercises versus control was evaluated in the subgroups by standardized mean differences (SMDs) and 95% confidence intervals (95% CIs). Heterogeneity between subgroups was tested using a chi-square test. HAQ = Health Assessment Questionnaire; VAS = visual analog scale; NA = not applicable.

there was a positive impact of exercises on quality of life, but no impact in established RA (disease duration ≥5 years). Pain responded in an opposite direction, with pain reduced if the duration was >5 years, but no effect if it was <5 years. Cardiorespiratory aerobic exercise conditioning had a positive impact on quality of life when performed <3 times per week, whereas it had no effect when performed ≥3 times per week. The duration of the individual session and exercise supervision also had an impact on quality of life. If the duration of the exercise session was >60 minutes there was a positive impact, whereas exercise sessions lasting ≤60 minutes had no effect. If exercise was supervised there was a positive impact, but there was no effect if the exercise program was home based and unsupervised. The entire program duration impacted pain. If the program lasted 3 months, less postintervention pain was improved, but it did not improve when the program

lasted more than 3 months. Methodologic quality had no impact on any of the variables, whereas publication date impacted the pain VAS results. Studies published after 2000 showed a positive effect on the VAS, whereas studies published before 2000 did not. Sensitivity analyses showed that the SMD and 95% CI were not substantially altered by removing any of the trials (data not shown).

**Publication bias.** We did not identify any publication bias for quality of life, pain, joint count, radiologic damage, and DAS28 assessments. Concerning the HAQ meta-analysis, both the Begg's test result (*P* = 0.045) and the Egger's test result (*P* = 0.017) were significant, indicating a potential bias. Inspection of funnel plots for the HAQ assessment revealed that studies with an important standard error, i.e., with a few patients, and a negative SMD,



i.e., showing better HAQ assessment in the control group than the intervention group, were lacking (see Supplementary Figure 2, available in the online version of this article at <http://www3.interscience.wiley.com/journal/77005015/home>).

**Clinical relevance.** Quality of life, HAQ, and pain VAS postintervention changes were considered clinically meaningful when they were greater than 0.2 (31). It was noteworthy that several clinical trials achieved such clinical significance on the HAQ (3,8). However, the SMDs were smaller than 0.5, indicating a small effect of aerobic exercise on each outcome measure (Figures 1–4).

## DISCUSSION

This systematic review and meta-analysis showed that cardiorespiratory aerobic exercises improve some of the most important RA patient outcomes: function, quality of life, and pain. Moreover, it appears that aerobic exercise decreases radiologic damage and pain. DAS28, joint count, compliance, and adverse events were similar in both groups, indicating that exercises were safe in stable RA. Only RCTs focusing on the efficacy of aerobic exercise in RA patients were considered in this review, creating two groups with similar demographic disease-related parameters and comparable treatments at baseline and providing a strong internal validity.

Although our review suggests that exercise, on its own, improves most disease outcomes, a few limitations should be emphasized. First, data were extracted from the literature by a single observer and although this extraction was supervised every two months by two other reviewers, a potential bias may exist. Second, there was some methodologic bias in most studies. Lack of blinding of outcome assessors, for instance, may cause bias. A recent study (32) emphasized differences in the physical function level of RA patients in different European countries with higher levels of physically active patients in northern European countries than in the South. We did not examine the influence of the baseline physical activity on either outcomes or heterogeneity, as this parameter was seldom reported. Since we focused on RCTs, this potential confounder was probably equally distributed in control and intervention groups, but we could not determine whether exercise programs were as effective with physically active patients as with patients without regular physical activity or without exercise program experience.

This meta-analysis suggests that aerobic exercise therapy is safe in stable RA. Appraisal of adverse effects during nonpharmacologic interventions is less stringent than during pharmacologic interventions, a fact explaining, at least partially, a lower detection of adverse events (33). Therefore, adverse events occurring during exercise programs may be underestimated. Similarly, data on compliance are more often described in pharmacologic treatment reports than in nonpharmacologic treatment reports. The rate of completers is probably a less accurate measurement of compliance than the percentage of the maximum number of sessions that could be attended. Unfortunately, only a

few studies reported this outcome measure, mostly in long-term intervention trials. Fatigability with exertion and cardiovascular adverse events are important proxies for exercise tolerance, which have not yet been accurately evaluated. According to Metsios et al, these two outcome measures deserve more attention in future trials (34).

The efficacy of exercise on pain assessed by a VAS, quality of life, disability assessed by the HAQ, and joint count was statistically significant, but the magnitude of the effect was small (SMD <0.5). However, most of these outcome measures were designed for monitoring patients in pharmacologic trials and may not be appropriate for the evaluation of physical interventions. Therefore, a small improvement of the HAQ or quality of life may reflect an inability of these indices to detect the effects of an exercise program rather than a failure of aerobic exercises to improve patients' health status (9,35,36). The efficacy of aerobic exercises on disability, quality of life, pain, and joint count should be more rigorously compared with conventional pharmacologic treatment in further investigations in order to determine their place in RA management.

Several lines of evidence suggested that any exercise is better than no exercise at all (32), but the exercise parameters (intensity, duration, frequency, and type) that result in better effects are not clearly defined. The ideal way of looking at the effect of exercise intensity, duration, frequency, and type would be to have an RCT comparing these parameters (head-to-head comparisons). Unfortunately, such data are sparse. In our meta-analysis, we performed subgroup analysis–based heterogeneity exploration as an alternative approach to evaluating the influence of patient characteristics or intervention parameters on the sizes of the treatment effect. Aerobic cardiorespiratory conditioning improved the HAQ in patients with class I–II functional status but did not ameliorate patients with more severe functional status. Both program duration and disease duration impacted pain, with better results in case of established RA and short-term programs, whereas data concerning quality of life suggested that exercise benefits more early RA patients than established RA patients. Supervised exercise and 60-minute exercise sessions performed biweekly or less had a greater effect on quality of life than home-based exercises and 30-minute exercise sessions performed more than 3 times per week, respectively. Similarly, Neuberger et al showed that patients taking part in a 12-week class exercise program experienced significant amelioration in disease-related parameters, whereas home-based exercise did not have that result, probably because patients in this group exercised at a lower intensity (29). Indeed, most of the studies reporting positive effects of exercises on quality of life were supervised intervention trials (3,20,24), whereas most of the studies in which this outcome was not modified were home-based exercises (25). It is likely that supervised exercises result in higher adherence to the exercise program and positive group enthusiasm, explaining the trend of higher SMDs in subsets of trials with supervised intervention. However, the impact of supervised dynamic exercise programs on work and on consumption of medical and of paramedical resources is unclear. Van den Hout et al suggested that supervised class exercises in the Rheumatoid

Arthritis Patients In Training cohort (37), which are more expensive than home-based interventions (3), provided insufficient improvement to justify the additional costs as a medicoeconomic issue.

An exercise program could be of particular interest to the elderly by reducing the risk of falls and fractures (38–40) and by improving the cardiovascular disease risk profile (41). Since a single RCT evaluated the efficacy of aerobic exercise in RA patients age >65 years, we were unable to look for heterogeneity of exercise efficacy or safety according to this parameter. Therefore, our results showing the benefit of aerobic exercises in middle-aged RA patients should not be generalized to the older RA population. However, Lyngberg et al (28) showed that an individually adapted training session performed at 50–70% of the maximal heart rate can be performed in elderly RA patients. Physiologic function capacity decreases linearly with aging (42,43). As a consequence, a baseline evaluation of physiologic function capacity and cardiovascular risk factors is mandatory in order to adapt exercise intensity to older RA patients. Moreover, stringent monitoring of adverse events as well as a progressive increase of exercise intensity appear appropriate in this population. A possible way to increase the compliance of older RA patients would be to perform “natural” aerobic exercise such as walking or cycling.

RA patients are dramatically physically inactive (32). This systematic review supports a more frequent recommendation of exercise to RA patients. Besides the positive effect of the intervention on patients’ psychological well-being, aerobic exercise should be considered as a safe therapy, the efficacy of which has been underestimated. The clinically meaningful and economic impact of such treatment must be investigated in further trials in order to clearly define the place of aerobic exercises in RA management.

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## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Mr. Baillet had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study conception and design.** Baillet, Zeboulon, Gossec, Juvin, Dougados, Gaudin.

**Acquisition of data.** Baillet, Bodin.

**Analysis and interpretation of data.** Baillet, Zeboulon, Gossec, Combescure, Juvin, Dougados.

## ROLE OF THE STUDY SPONSOR

Abbott France organized a meta-analysis methods workshop but played no further role in the project. Abbott France did not participate in drafting the article, did not see the manuscript before submission; and in particular, Abbott France did not choose the subject and did not participate in the study design,

the data collection, or the data analysis. This article was not submitted for approval to Abbott France.

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## **PARTIE II**

### **Intérêt du renforcement musculaire dans la polyarthrite rhumatoïde : Analyse systématique de la littérature et méta-analyse d'essais randomisés contrôlés**

## **PARTIE II : SYNOPSIS DU DEUXIEME ARTICLE**

### Introduction :

Nos précédentes études ont suggéré l'intérêt de d'entraînement aérobie chez les patients atteints de PR. L'objectif de cette deuxième étude était de déterminer l'effet du renforcement musculaire sur la force musculaire, la fonction, la marche, la douleur, et l'activité de la maladie des patients atteints de PR.

### Patients et Méthodes :

Nous avons conduit une analyse systématique de la littérature de tous les essais randomisés contrôlés évaluant le renforcement musculaire dans les bases de données Medline, Cochrane et EMBase (jusque novembre 2009) par 2 évaluateurs indépendants. L'accord entre ces 2 lecteurs était apprécié au moyen de l'indice kappa. Le groupe intervention devait bénéficier d'exercices de renforcement musculaire alors que le groupe contrôle ne bénéficiait d'aucun exercice. La variation des données suivantes a été étudiée avant et après l'intervention : la fonction sur le Health Assessment Questionnaire (HAQ), la vitesse de marche, l'échelle visuelle analogique douleur (EVA), la force musculaire, le compte articulaire, la vitesse de sédimentation, le nombre de patients sortis de l'étude et le nombre d'effets indésirables. La qualité méthodologique de chaque étude était analysée sur le score de Jadad (0-5).

Une méta-analyse par le modèle de l'inverse de la variance a été effectuée. Les résultats ont été exprimés en différence de moyenne pondérée (weighted mean difference, WMD) pour les variables quantitatives et en risque relatif (RR) pour les variables qualitatives ainsi que leurs intervalles de confiance à 95% (IC95%). Les WMD et RR ont été agrégés en comparant le groupe actif au groupe contrôle. Les WMD étaient comparées à la plus petite variation cliniquement pertinente (smallest detectable change SDD ou minimally clinically important difference MCID). Une analyse de sous-groupe a été conduite pour identifier un facteur d'hétérogénéité entre les études. Un biais de publication a été recherché par analyse graphique et par les tests statistiques de Begg et Egger.

### Résultats :

10 essais randomisés contrôlés, incluant 547 patients, ont été analysés. L'accord entre les 2 évaluateurs pour la sélection des articles était de 98%, kappa=0,85, IC95% [0,78, 0,93]. Le score moyen de Jadad était  $2,3 \pm 0,6$ , avec un accord inter-observateur de 88% (kappa = 0,60, IC95% [0,47, 0,73]). Le renforcement musculaire améliorait la force isocinétique (WMD = 23,7%, IC95% [11,0, 36,4],  $p = 0,0002$ ), isométrique (WMD = 35,8%, IC95% [24,4, 47,1],  $p < 0,00001$ ) ainsi que la force de préhension (WMD = 26,4%, IC95% [12,3, 40,5],  $p = 0,0003$ ). L'amélioration de la fonction évaluée par le HAQ était à la fois statistiquement significative et cliniquement pertinente dans le groupe intervention par rapport au groupe contrôle (WMD = -0,22, IC95% [-0,35, -0,10],  $p = 0,0006$ ). Le renforcement musculaire avait un impact positif sur la vitesse de la marche (WMD = -1,90 s, IC95% [-2,95, -0,85],  $p = 0,0004$ ) et sur la vitesse de sédimentation à la première heure (WMD = -5,17 mm, IC95% [-8,77, -1,58],  $p = 0,005$ ). L'exercice physique était bien toléré ; aucune différence entre les 2 groupes n'a été constatée en ce qui concerne le nombre de patients sortis d'étude (RR=0,95, IC95% [0,61, 1,48],  $p=0,82$ ) ou sur la survenue d'évènements indésirables (RR=1,08, IC95% [0,72, 1,63],  $p = 0,87$ ). Les caractéristiques démographiques n'influençaient pas les résultats. Les entraînements les plus intensifs avaient tendance à être plus efficaces. Les résultats étaient robustes lors de l'analyse de sensibilité. Nous n'avons pas mis en évidence de biais de publication.

### Discussion :

Nous avons pu démontrer un effet positif du renforcement musculaire sur la force, le HAQ, la vitesse de marche sans augmenter la survenue d'effets indésirables. Le faible nombre d'études incluses et leur qualité méthodologique modérée nous incitent à conduire de nouveaux essais ciblant notamment des populations plus fragiles et appréciant l'intérêt sur d'autres critères d'évaluation tels que la qualité de vie, la survenue de chutes et de fractures, les évènements cardiovasculaires et l'impact médico-économique.

### Conclusion :

Le renforcement musculaire, efficace et bien toléré dans la PR, doit être proposé plus fréquemment aux patients.

## **EFFICACY OF RESISTANCE EXERCISES IN RHEUMATOID ARTHRITIS: META-ANALYSIS OF RANDOMISED CONTROLLED TRIALS**

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Key messages

1. Resistance exercise in rheumatoid arthritis is safe and improves muscle strength, disability and walking performance.
2. The improvement on disability is clinically relevant.

## ABSTRACT

**Background:** The objective of this meta-analysis was to evaluate the efficacy of resistance exercises in Rheumatoid Arthritis (RA) patients.

**Methods:** A systematic literature search was performed using Medline, Embase and Cochrane databases through November 2009 and in abstracts presented at rheumatology scientific meetings over the last 3 years. Randomised controlled trials comparing resistance exercise-based therapy to interventions without resistance exercise for the treatment of RA patients were included. Outcomes studied were post-intervention, disability on the Health Assessment Questionnaire (HAQ), functional capacity assessed by walking speed, pain on the Visual Analogue Scale (VAS), joint count, isometric, isokinetic and grip strength. Efficacy was assessed by weighted mean differences (WMD), and tolerance was assessed by relative risk (RR). Data were pooled using the inverse of variance model, and heterogeneity was tested.

**Results:** 10 randomised controlled trials, including 547 patients, met study inclusion criteria. The mean Jadad score was  $2.3 \pm 0.6$ . Resistance exercises significantly improved isokinetic strength (WMD=23.7%,  $p < 0.001$ ), isometric strength (WMD=35.8%,  $p < 0.001$ ) and grip strength (WMD=26.4%,  $p < 0.001$ ), and HAQ (WMD=-0.22,  $p < 0.001$ ). Exercise also had a positive impact on the 50 feet walking test (WMD=-1.90s,  $p < 0.001$ ) and ESR (WMD=-5.17,  $p = 0.005$ ). Withdrawals (RR=0.95, 95%CI [0.61, 1.48]) and adverse events (RR=1.08, 95%CI [0.72, 1.63]) were well-balanced in both groups. Patient and exercise characteristics did not influence the results. Subgroup analysis revealed a trend toward higher efficacy associated with high intensity programmes.

**Conclusion:** Resistance exercise in RA is safe; the improvement in most outcomes was statistically significant and possibly clinically relevant for RA disability.

**Keywords:** Rheumatoid Arthritis, Strengthening exercise, Dynamic Exercise Program.



## INTRODUCTION

Joint involvement in Rheumatoid Arthritis (RA) often leads to deformities and muscle atrophy, which dramatically impact RA management and outcomes. Specifically, impairment in range of motion and muscle strength increase RA-associated disability, widely impacting patient quality of life and leading to increased health care costs, both for the patient and the health care system. In addition, the decrease in joint mobility and muscle strength prevents RA patients from performing regular physical activities. Therefore RA patients are often physically inactive [1], leading to further muscle deconditioning and exercise intolerance.

Despite the significant impact of pharmaceutical interventions, physical therapy and exercise training remain an important part of RA management [2]. Moreover, given that cardiovascular events are an important issue in RA outcomes, improving cardiovascular risk [3] through aerobic exercise seems to be the most relevant adjuvant therapy in RA management [4]. Indeed, aerobic exercises have been shown to improve cardiovascular fitness and patient quality of life, while reducing RA associated disability and pain [5].

However, use of resistance exercise therapy for RA patients is still controversial, because its effects on cardiovascular risk are still a concern [6]. Moreover, although some previous studies have shown a statistically significant impact on RA disability [7-9], others have suggested that this improvement is not statistically significant [10] or clinically relevant [11]. Similarly discrepancies were observed between studies reporting a positive impact from exercise on functional capacity [11], versus others which did not find such a positive effect [8, 10]. These disparities are likely due to the sample size variations, and the fact that most of the studies evaluating resistance exercises only addressed changes in muscle strength. In fact few studies addressed the efficacy of resistance exercise based therapy for RA patients with respect to pain, disease activity, functional capacity, quality of life and structural damage; thus the effects of this therapy remain unclear. Therefore, we conducted a systematic review of the literature, to determine whether resistance exercise effectively improves the above-mentioned parameters in RA. Finally, we assessed whether this treatment addition is clinically relevant, and evaluated its dependence on exercise modalities and/or patient characteristics.

## **METHODS**

Meta-analysis was conducted according to Cochrane Collaboration guidelines [12].

### **Type of intervention**

Resistance exercises were (i) repetitive exercises (ii) specifically designed to improve muscle strength (iii) through increased or adjusted resistance. Resistance was restricted to (iv) 30-100% of the maximal load or adjusted by the therapist, (v) without substantial exercise in the control group.

Non-aerobic rehabilitation was defined as: “static”, “range of motion”, “isometric”, “seated immersion”, “relaxation”, “stretching”, “no attention” or “usual care”. Trials which included aerobic exercise in the control group were not considered in this study.

### **Search strategy**

An extensive search of PubMed, Embase and the Cochrane Central register of RCTs (until November 18th, 2009) was conducted by 2 independent reviewers (AB and MV). The following keywords were used to retrieve data from the Pubmed and Cochrane Arthritis databases: Rheumatoid"[Mesh] AND ("strengthening"[tw] OR "strength"[tw]); and the limit “clinical trial” was applied. Keywords for Embase database searches were: 'strength'/exp OR strengthening OR 'exercise'/exp AND ('arthritis'/exp OR rheumatoid), with 'controlled clinical trial'/lim as the limit. A hand search of references was also conducted from relevant articles, review papers, and abstracts presented at the American College of Rheumatology's (ACR) annual scientific meetings, the European League Against Rheumatism's (EULAR) annual congress, and the French Society of Rheumatology's (SFR) scientific meetings published over the 5 past years. A search on the ClinicalTrials.gov website was also performed to identify randomised studies not yet published.

### **Selection**

Inclusion criteria were: (i) randomised controlled trials (RCT), which evaluated (ii) resistance exercise (iii) in adult patients diagnosed with RA, (iv) as defined by the American Rheumatism Association [13] or ACR criteria [14]. Exclusion criteria were: (i) post-surgery rehabilitation studies, and (ii) articles written in a language other than English or French.

## **Study quality assessment**

Two independent authors (AB and MV) assessed the methodological quality of each study included in the present meta-analysis using the Jadad scale [15], ranging from 0 to 5 (a high score indicating high quality). When disagreements remained after discussions between both reviewers, a third reviewer (PG) was consulted regarding inclusion of the study.

## **Data extraction**

Two independent investigators (AB and MV) selected the articles and collected the data using a pre-determined form, which included: the study design (randomisation procedure, blinding, follow-up period and intention-to-treat analysis), patient characteristics (number, age, gender, disease duration, functional status, rate of rheumatoid factor positive patients and withdrawals), and intervention parameters (duration of each exercise session, overall duration of the intervention, exercise type, frequency, number of repetitions, and intensity or maximal load). When disagreements remained after discussions between both reviewers, a third reviewer (PG) was consulted.

## **Outcomes**

In the present study, we report tender joint counts, swollen joint counts, pain and disability. The safety of resistance exercises was assessed using withdrawals and adverse events. The following outcomes were extracted from the publications:

**Muscle strength:** Isokinetic strength was measured as the peak torque of the knee extensor at a constant speed of 60°/s; isometric and grip strength were determined as the maximal or submaximal voluntary contraction, measured using a dynamometer.

**Disability:** assessed using the Health Assessment Questionnaire (HAQ) [16].

**Functional capacity:** assessed by walking speed, the 50 feet walking test (time required to walk a distance of 50 feet), and the aggregate functional performance time [17]. When results were expressed as walking speed, we calculated the time to walk a distance of 50 feet.

**Disease activity score:** DAS 28 [18].

**Joint count:** calculated from the number of swollen joints, tender joints and Ritchie index [19], converted to a percent scale.

*Pain on visual analogue scale (VAS).*

*Erythrocyte sedimentation rate:* ESR measured at one hour.

*Exercise tolerance:* evaluated by the number of subjects completing the exercise, exercise attendance and adverse events (whether or not related to RA and exercise).

*Radiological damage:* assessed according to the Larsen scoring system [20].

Data abstraction was performed using baseline and post-intervention means, as well as measures of dispersion. We compared post-intervention means between both groups, with the exception of HAQ and muscle strength, for which we also compared the change from baseline values after completion of the intervention programme, because the randomisation procedure generated comparable groups for these baseline outcome measures at baseline. When median values were reported instead of mean values, the median was analysed as a mean. Because measures of dispersion for change were not always available, a conservative estimate was made from baseline data, and converted into a standard deviation. When a trial was reported in several publications, the more informative publication was included in the meta-analysis.

When disagreements remained after discussions between both reviewers, a third reviewer (PG) was consulted regarding outcome extraction and Jadad scoring.

### **Statistical analysis**

The efficacy of resistance exercise was assessed in each study, by calculating the weighted mean difference (WMD) and 95% confidence interval (95% CI). Tolerance was expressed as the relative risk for an adverse event or withdrawal (an  $RR > 1$  indicates that the event is more likely to occur in the resistance exercise group than in the control group). Results from individual trials were pooled by meta-analysis, using the inverse of the variance method with a random effect. When a statistically significant impact was found, WMDs were compared with published values for minimum clinically important differences (MCID), in order to identify clinically relevant improvements. The heterogeneity of outcomes between studies was examined using an extension of the Q statistic,  $I^2$  (and its 95% CI), which was considered to be statistically significant at values  $>50\%$  [21]. Inter-reviewer reproducibility for study selection, data extraction and methodological quality assessment was calculated. Inter-reviewer reproducibility was considered to be moderate for kappa coefficients ranging from 0.21 to 0.60; good for kappa coefficients  $>0.60$ ; and excellent for kappa coefficients  $\geq 0.80$ .

Meta-analyses were performed with Review Manager 5 (RevMan Version 5.0., Denmark), while additional statistical analyses were conducted with StatsDirect (StatsDirect statistical software, England).

### **Sensitivity analysis and heterogeneity assessment**

Sensitivity analysis was conducted to evaluate the robustness of the meta-analysis, by assessing the influence of an individual study on the pooled results; this was accomplished by examining the effect of deleting each study individually from the meta-analysis. We also assessed heterogeneity in HAQ changes, by combining studies into 2 subgroups according to trial design (those published before or after 2000; and Jadad scale  $\leq 2$  or  $\geq 3$ ), disease duration (mean disease duration  $< 2$  years or  $\geq 2$  years), and intervention parameters (supervised or home-based; overall duration of the intervention  $\leq 6$  or  $> 6$  weeks; exercise frequency  $\leq 2$  or  $> 2$  times/week; intensity of exercise  $\leq 80\%$  or  $> 80\%$  of the maximal load). Heterogeneity between subgroups was tested using a Chi<sup>2</sup>-test [22].

### **Publication bias**

Publication bias was assessed using funnel plot analysis, Begg's test and Egger's test.

## RESULTS

### Trial flow

The review process is summarised in **Figure 5 additional material**. In total, 693 abstracts were identified by database searching, and an additional 3 articles by hand searching. Of these, 61 full-text articles were analysed and 10 articles were finally included in this study [8-11, 23-28]. Inter-reviewer reliability was good for abstract selection ( $\kappa=0.85$ , 95%CI [0.78, 0.93], 98% agreement).

### Study characteristics

Intervention parameter characteristics are summarised in Table 1. The mean  $\pm$  standard deviation Jadad score was  $2.3 \pm 0.6$ , and 7 trials displayed a Jadad score  $\leq 2$ . Of the 10 studies analysed: 3 studies focused on quadriceps resistance exercises [9, 23, 25]; 5 studies evaluated the efficacy of upper and lower extremities training, with [8, 26] or without trunk strengthening [10, 11, 27]; 1 study evaluated the impact of shoulder strengthening [28]; and 1 study evaluated hand [24] strengthening. Exercises were supervised in 5 studies [9-11, 23, 27]. The control group performed range of motion exercises in 3 studies [10, 26, 27]; non-aerobic exercises in 1 study [28]; and usual care in 6 studies [8, 9, 11, 23-25].

### Patient characteristics

The meta-analysis included 10 studies, comprising 547 patients (282 in the resistance exercise group and 265 in the control group). Both groups were similar in terms of age, disease duration, sex ratio, proportion of patients completing the program, rate of rheumatoid factor positive patients, and DMARD treatments (**Table 3 additional material**). The mean age in the studies ranged from 41 to 62 years. Only 2 studies specifically included early RA patients [25, 26]. For the 8 studies for which gender was reported, 47.6% to 100% were female. The rate of rheumatoid factor positive patients was reported in 3 studies (range 54.3-88.2%).

### Meta-analysis

Inter-reviewer reliability was moderate for data extraction and Jadad scoring ( $\kappa=0.60$ , 95%CI [0.47, 0.73], 88% agreement).

### Efficacy

Data on isokinetic strength changes were available for 3 studies (76 patients in the intervention group and 72 patients in the control group), with a positive effect from exercise on this outcome (WMD=23.7%, 95% CI [11.0%, 36.4%],  $p<0.001$ ;  $I^2=0\%$ , 95% CI [0%, 73%]). Resistance exercise was also found to enhance isometric strength changes (WMD=35.8%, 95%CI [24.4%, 47.1%],  $p<0.001$ ;  $I^2=68\%$ , 95% CI [0%, 86%]). In total, 5 studies, with 153 patients in the intervention group and 147 patients in the exercise group, evaluated isometric. Data on grip strength changes was pooled for 4 studies, comprising 126 patients in the resistance exercise group and 117 patients in the control group (**Figure 1**), and a positive impact on this outcome was demonstrated (WMD=26.4%, 95% CI [12.3%, 40.5%],  $p<0.001$ ;  $I^2=0\%$ , 95% CI [0%, 68%]).

A post-intervention mean  $\pm$  SD for HAQ was extractable from 7 studies [9-11, 23-27], comprising 187 patients in the intervention group and 179 in the control group (WMD=-0.17, 95%CI [-0.38, 0.04],  $p=0.12$ ;  $I^2=47\%$ , 95% CI [0%, 77%]) (**Figure 2**). Because baseline HAQ scores were substantially higher in the intervention group than in the control group in 2 studies [9, 27], we also calculated a WMD for HAQ variation (-0.22, 95% CI [-0.35, -0.10],  $p<0.001$ ;  $I^2=36\%$ , 95% CI [0%, 69%]). for 9 studies, comprising 289 patients in the exercise group and 324 patients in the control group.

Functional capacity was assessed for 5 studies, comprising 137 patients in the intervention group and 138 patients in the control group. Three studies reported results for the 50 feet walking test [8, 9, 27], while 1 study recorded either aggregate functional performance time, or 30 meters walk speed [26]. Resistance exercise was associated with a positive effect on functional capacity (WMD=-1.90 s, [-2.95 s, -0.85 s],  $p<0.001$ ;  $I^2=35\%$ , 95% CI [0%, 75%]).

Data on joint counts were available in 6 studies, comprising 201 patients in the intervention group and 189 patients in the control group. The Ritchie articular index was reported in 4 trials [7, 8, 24, 28], the swollen joint count in 1 study [10] and the tender joint count in 1 study [23]. Resistance exercise was found to decrease joint count (WMD=-5.36%, 95% CI [-9.00%, -1.72%]  $p=0.004$ ;  $I^2=73\%$ , 95% CI [12%, 86%]). Only 2 studies reported a DAS28 [10, 27]. No impact from resistance exercise on DAS28 was demonstrated in any of these studies.

In total, 5 studies evaluated the impact of resistance exercises on VAS pain, comprising 144 patients in the intervention group and 140 patients in the control group (**Figure 3**); a trend toward a small positive effect on VAS pain was observed (WMD=-4.1mm, 95% CI [-11.0, 2.7],  $p=0.24$ ;  $I^2=54\%$ , 95% CI [0%, 82%])

ESR was recorded in 3 studies, comprising 133 patients in the resistance exercise group and 125 patients in the control group; and a significant decrease in ESR was found in the intervention group (WMD= -5.17mm, 95%CI [-8.77, -1.58],  $p=0.005$ ;  $I^2=0\%$ , 95% CI [0%, 73%]) (**Table 5 additional material**).

### Safety

Seven studies [8-11, 23, 25, 26], consisting of 199 patients in the resistance exercise group and 172 patients in the control group, reported withdrawals: 37 (18.6%) patients in resistance exercise group and 28 (16.3%) patients in the control group (RR=0.95, 95%CI [0.61, 1.48],  $p=0.51$  ;  $I^2=0\%$ , 95% CI [0%, 50%]) (**Figure 4**).

Seven studies [8-10, 23, 25, 26, 28], comprising 197 patients in the resistance exercise group and 181 patients in the control group, reported adverse events; however, no statistical difference was found in the number of adverse events (RR=1.08, 95%CI [0.72, 1.63],  $p=0.72$ ;  $I^2=0\%$ , 95% CI [0%, 59%]) between both groups for both RA-related and RA-unrelated exercise adverse events. Notably, no difference was found for cardiovascular disease, flares or psychological distress (**Table 4 additional material**). Only 2 trials reported attendance [10, 11, 27], ranging from 73 to 82% (**Table 1**).

### Heterogeneity and sensitivity analysis

Heterogeneity between the studies was moderate according to the outcome measures. Disease duration, publication date, exercise supervision, exercise duration and exercise frequency and had negligible impact on HAQ change (**Table 2**). However, methodological quality and exercise intensity were found to slightly impact the results, with a trend toward higher efficacy for studies with a lower Jadad score and higher exercise intensity.

### Clinical Relevance

Although muscle strength improvement (ranging from 23.7% to 35.8%) appears to be important, it is difficult to determine whether it is clinically relevant, because the MCID for this outcome was found to vary widely across the studies [29]. The positive impact of resistance exercise on HAQ (WMD=-0.25, 95% CI [-0.37, -0.13]) was higher than the MCID [30], whereas the benefits of resistance exercise on pain ESR and VAS are unlikely to be clinically relevant. The impact of functional capacity on the 50 feet walking test was greater than the intra or inter-rater reliability [32].



## Publication bias

We did not identify any publication bias (Figures 6 additional material).

## DISCUSSION

In this systematic review and meta-analysis, we show that resistance exercise decreases disability, functional capacity impairment and joint count. The positive impact on both functional capacity and disability is likely to be clinically relevant. Assessment of heterogeneity based on subgroup analysis did not identify any significant influence from patient or intervention characteristics on the sizes of the treatment effect. However, a trend toward higher efficacy was observed for studies with resistance exercise  $\geq 80\%$  maximum load. Several studies suggested that supervised aerobic exercises were more efficient than home-based exercises [5, 33]. However, our subgroup analysis results do not suggest that supervised exercises are associated with better results than home-based exercises. Further randomised controlled studies are required to determine whether supervised exercises are clinically relevant, taking into consideration both patient improvement and the additional costs of supervision.

Unfortunately, several important issues were beyond the scope of this meta-analysis. First, improvements in neuromuscular function may decrease the risk of falls and fractures, which is of particular interest given the significant risk of osteoporotic fractures for RA patients. In fact, a reduction in the number of falls and fractures after exercise programmes has been suggested in the elderly population in general [34-36], but this has not been confirmed in the RA patient population. A single study concluded that the effect of resistance exercise on bone mineral density is small [26]. Second, the medico-economic impact of resistance exercises for the treatment of RA patients has not been evaluated to date. Therefore, further studies are required to examine this issue, and to determine whether resistance exercise actually improves patient quality of life and minimises structural damage. Third, the long-term maintenance of the positive effects gained from resistance exercise has not been extensively evaluated, and remains controversial. For example, Van den Ende et al. reported that post-intervention muscle strength improvements only lasted for a few weeks; while, in contrast, Hakkinen et al. suggested that the long-term benefits of strength exercises were maintained according to outcome measures [37]. A possible explanation for this discrepancy may be differences in physical activity levels after cessation of the intervention program. Therefore, maintenance of a structured physical activity program after intervention seems to be critical for long-term benefits, because the effects of detraining occur early [38]. Finally, the

molecular mechanisms behind the beneficial effects of resistance exercise were not explored in this meta-analysis. Resistance training is associated with anabolic effects in muscle cells, through activation of the Akt/mTor pathway [39]. In addition, local production of IGF-1 [40] and growth factors in response to muscle contraction plays a key role, because it is a powerful activator of this pathway. The anti-inflammatory effects of exercise may also contribute to the decrease in ESR, and the beneficial effects observed on joints. Nevertheless, the consequences are likely important in resistance exercises [27] and cardiorespiratory fitness for both RA [41] and ankylosing spondylitis patients [42].

Although results from this meta-analysis are promising, this study is associated with some potential limitations. First, only 2 studies evaluated the benefit of resistance exercises in early RA, and most of the studies including middle-aged RA patients. Thus, our results should not be generalised to the older RA population, who are more likely to suffer from sarcopenia, and may benefit the most from resistance exercise. Second, information about previous exercise programme experience or current physical activity levels were never reported. Although we focused on RCT, a possible difference in physical activity levels between the intervention and control group cannot be ruled out. Third, most of the studies included in this met-analysis did not display high methodological quality. Potential sources of bias included inadequate adverse reporting [43] and blinding procedures. However, in physical intervention studies, complete blinding procedures are nearly impossible. Moreover, outcome measures extrapolated from pharmacological evaluation studies are probably not appropriate for physical intervention studies. For example, HAQ evaluates upper extremities, while resistance exercises mainly improve limb function [38]. Furthermore, adverse events were probably not thoroughly reported [44], because there is no consensus definition. Therefore, the tolerance of resistance exercise was possibly overestimated, especially among the older population. Adverse events should be clearly defined, in order to better report them in future trials.

Despite the fact that physicians do not often recommend resistance exercise for RA patients, this systematic review suggests that this type of physical intervention is safe and offers a clinically significant amelioration of functional capacity and disability. Beside its anti-inflammatory effects [45], an increasing body of evidence suggests that resistance exercise decreases cardiovascular risk factors [45], possibly to a greater extent than aerobic exercise [46]. However, the most effective proportion of aerobic and resistance exercise for the treatment of RA patient requires further evaluation.

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**TABLE 1. STUDY CHARACTERISTICS**

Author	Country	Jadad	ITT	Function	Intervention group								Control group	
					n=	exercise type	max load	repetitions	frequency/wk	duration min	length wk	attendance %	n=	comparator
Bearne L, 2002	UK	3	yes	nr	47	Supervised quadriceps strengthening	100	4x6	2	30-45	5	nr	46	Usual care
Boström A, 1998	Sweden	3	yes	ACR I-II	24	Non-supervised shoulder Strengthening	30	1x30	3	40-60	10	nr	21	Non aerobic exercises
Buljina A, 2001	Bosnia	2	unclear	nr	50	Hand resistance exercises	85	1x5	daily	20-30	3	nr	50	Usual care
Flint-Wagner HG, 2009	USA	1	no	ACR I-II	16	Supervised leg and arm exercises	90	2x6-8	3	75	16	82	8	Usual care
Hakkinen A, 2001	Finland	3	no	nr	35	Non-supervised trunk, leg and arm exercises	50-70	2x8-12	2	30-45	104	nr	35	ROM exercises
Hakkinen A, 1997	Finland	2	unclear	nr	21	Non-supervised quadriceps strengthening	40-80	2x15-30 to 3x6-12	2 to 3	nr	24	nr	18	Usual care
Komatireddy GR, 1997	USA	2	no	ACR II-III	25	Non-supervised trunk, leg and arm exercises	30-40 ##	1x15-30	2	20-27	12	nr	24	Usual care
Lemmey A, 2009	UK	2	unclear	ACR I-II	13	Supervised leg and arm exercise	80	3x8	2	nr	24	73	15	ROM exercises
Mc Meeken J, 1999	Australia	2	unclear	nr	17	Supervised quadriceps strengthening	70	4x5	≈2	45	6	nr	18	Usual care
Van den Ende CH, 2000	Netherlands	3	yes	nr	34	Supervised quadriceps and shoulder strengthening	60	3x5	3	15	~4	nr	30	ROM exercises

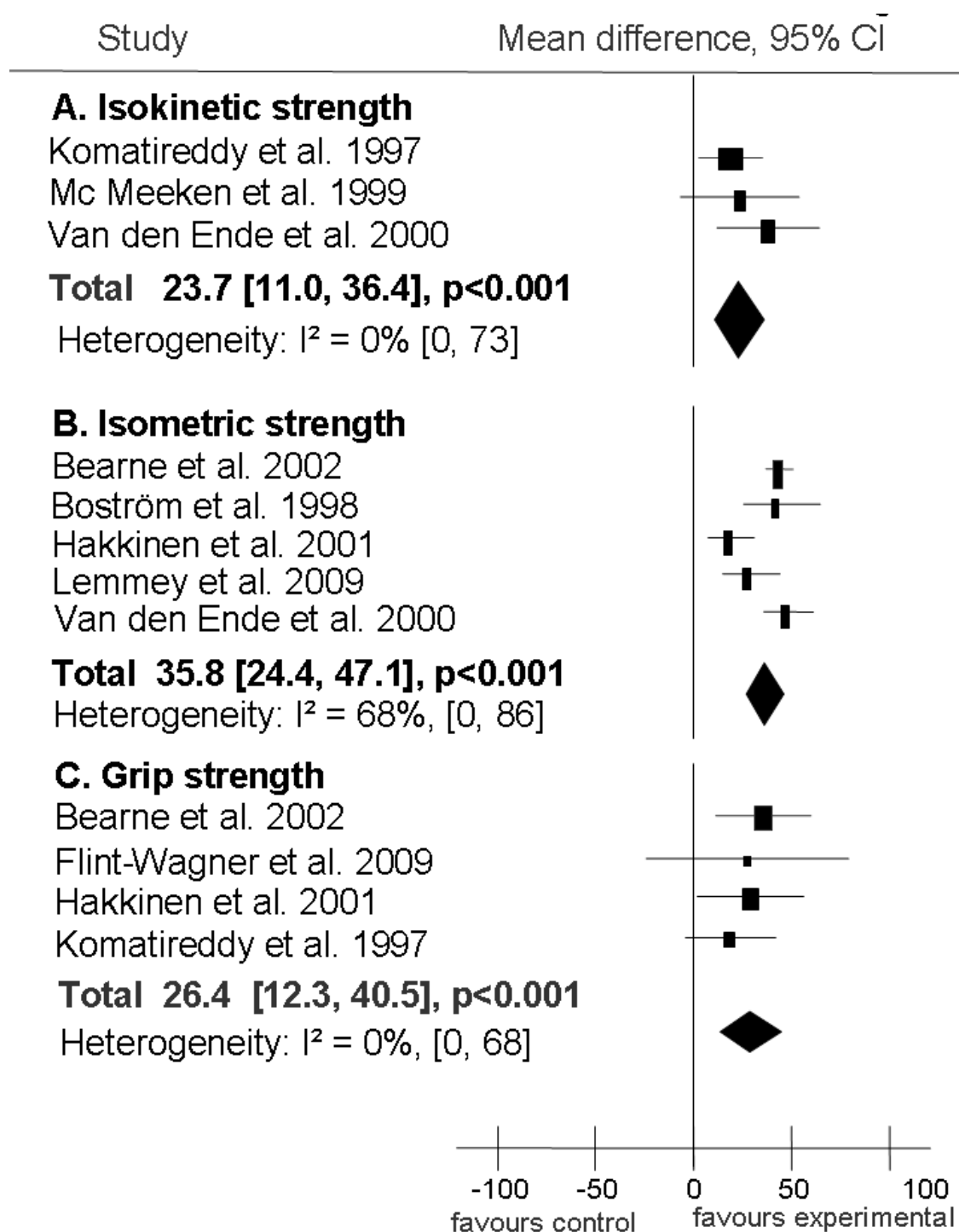
ITT= intention-to-treat analysis; ROM=range of motion; max=maximal; nr=not reported/inapplicable; ACR=American College of Rheumatology; wk=weeks. ## patients were instructed to exercise at 3 to 4 on a 1-10 scale.

**TABLE 2. HETEROGENEITY EXPLORATION**

	WMD, [95%CI]	I <sup>2</sup>	WMD, [95%CI]	I <sup>2</sup>	P value
<b>Disease duration</b>					
early vs. established RA	-0.12 [-0.32, 0.08]	26%	-0.28 [-0.45, -0.11]	74%	p=0.52
<b>Publication date</b>					
before vs. after 2000	-0.27 [-0.47, -0.07]	57%	-0.18 [-0.37, 0.00]	4%	p=0,99
<b>Methodological quality</b>					
Jadad ≤2 vs. >2	-0.34 [-0.58, -0.10]	40%	-0.14 [-0.24, -0.05]	0%	p=0,09
<b>Exercise supervision</b>					
Home-based vs. supervised	-0.20 [-0.43, 0.03]	64%	-0.30 [-0.46, -0.13]	0%	p=0,12
<b>Exercise duration</b>					
≤6 weeks vs. > 6 weeks	-0.19 [-0.29, -0.09]	3%	-0.25 [-0.58, 0.08]	64%	p=0,93
<b>Exercise frequency</b>					
≤ twice vs. >twice a week	-0.22 [-0.43, -0.02]	30%	-0.24 [-0.43, -0.05]	49%	p=0,62
<b>Exercise intensity</b>					
≤ 80% vs. > 80% of the max load	-0.19 [-0.37, -0.01]	53%	-0.33 [-0.52, -0.14]	0%	p=0,10

The efficacy of resistance exercises *versus* control was evaluated in the subgroups by weighted mean differences (WMD) and 95% confidence interval [95% CI]. Heterogeneity between subgroups was tested using a Chi<sup>2</sup>-test.

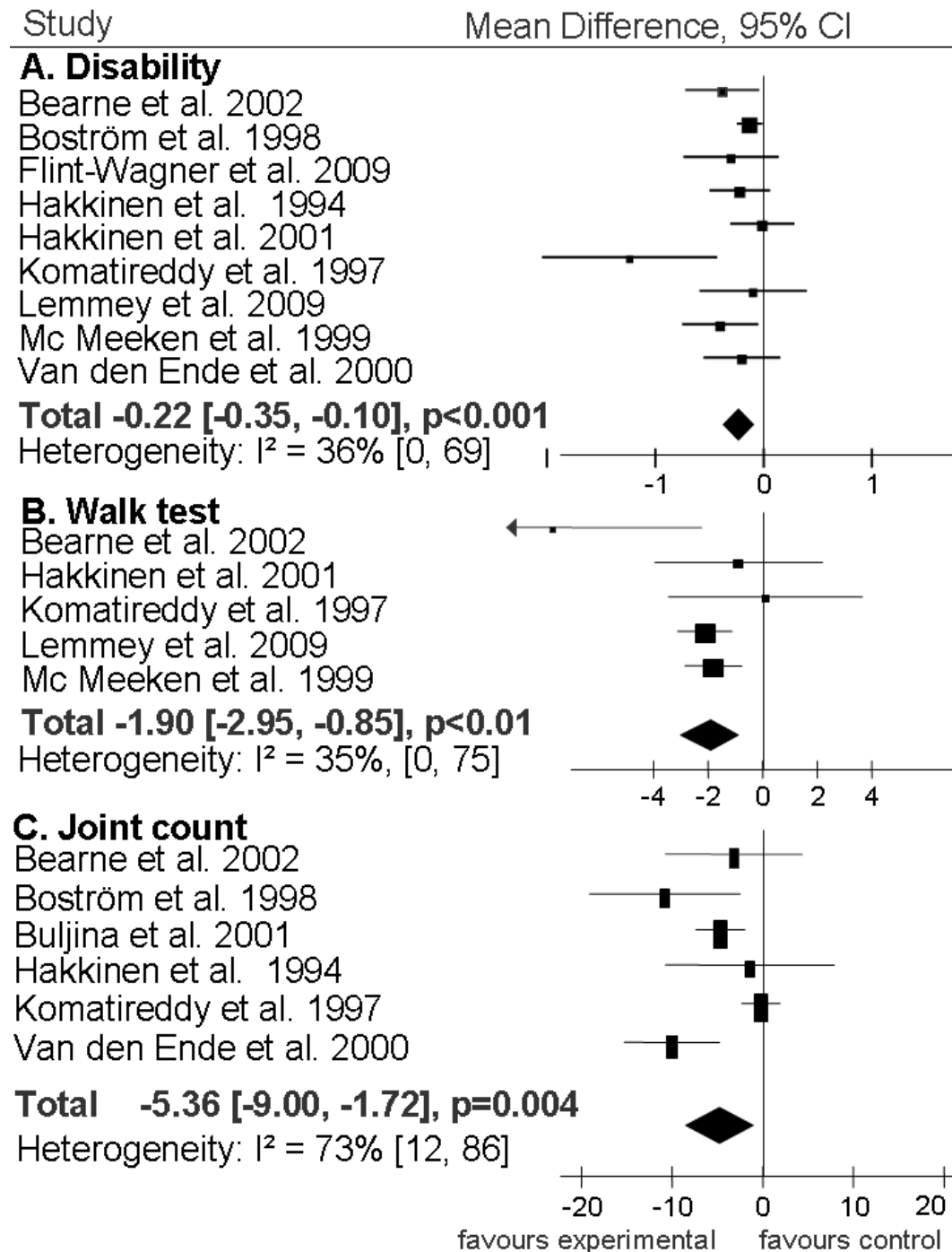
**FIGURE 1. INFLUENCE OF RESISTANCE EXERCISES ON STRENGTH.**



Data concerning isokinetic strength (A), isometric strength (B) and grip strength (C) were pooled using inverse variance weighting and random effect methods. 95% CI=95% confidence interval.

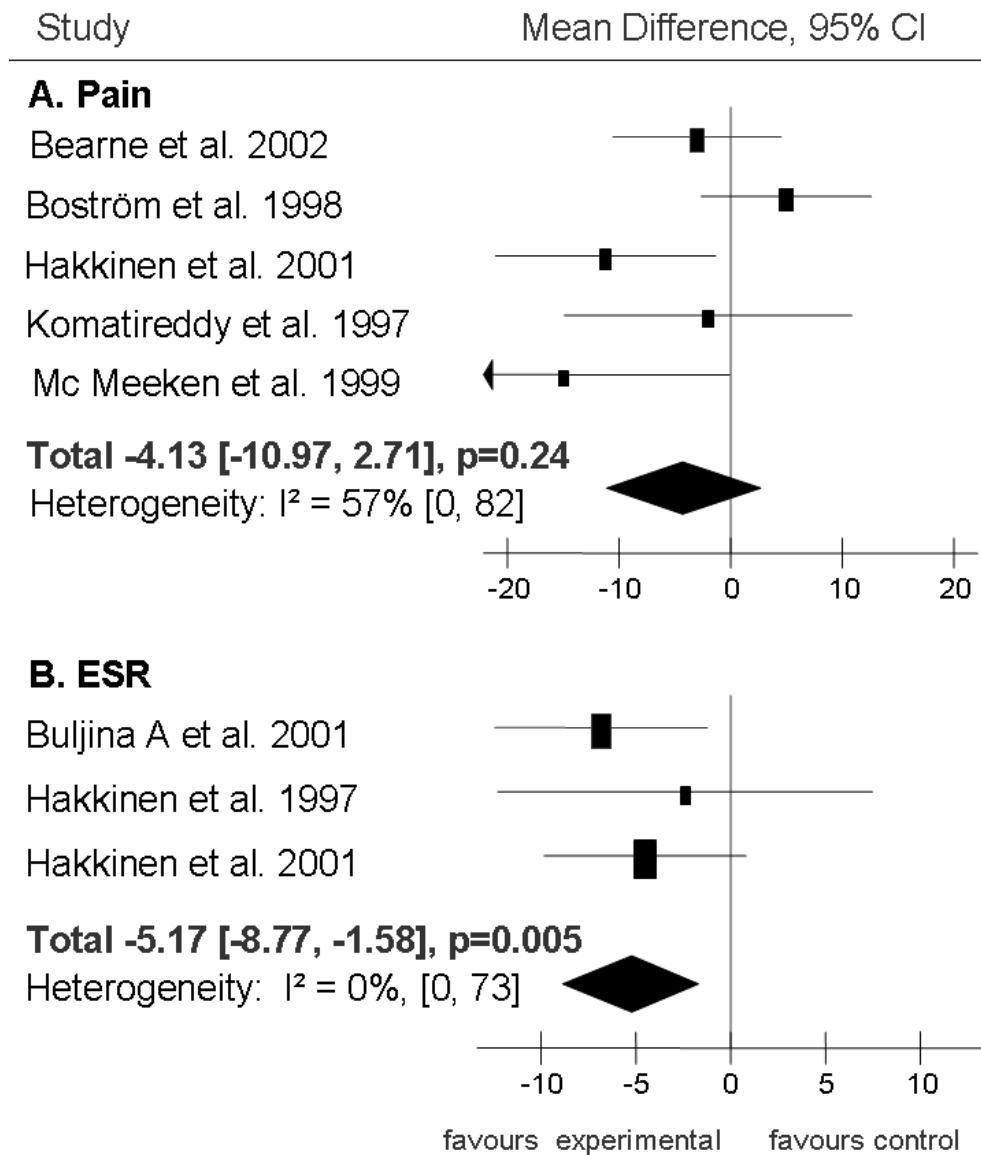


**FIGURE 2. INFLUENCE OF RESISTANCE EXERCISES ON DISABILITY, FUNCTIONAL CAPACITY AND JOINT COUNT.**



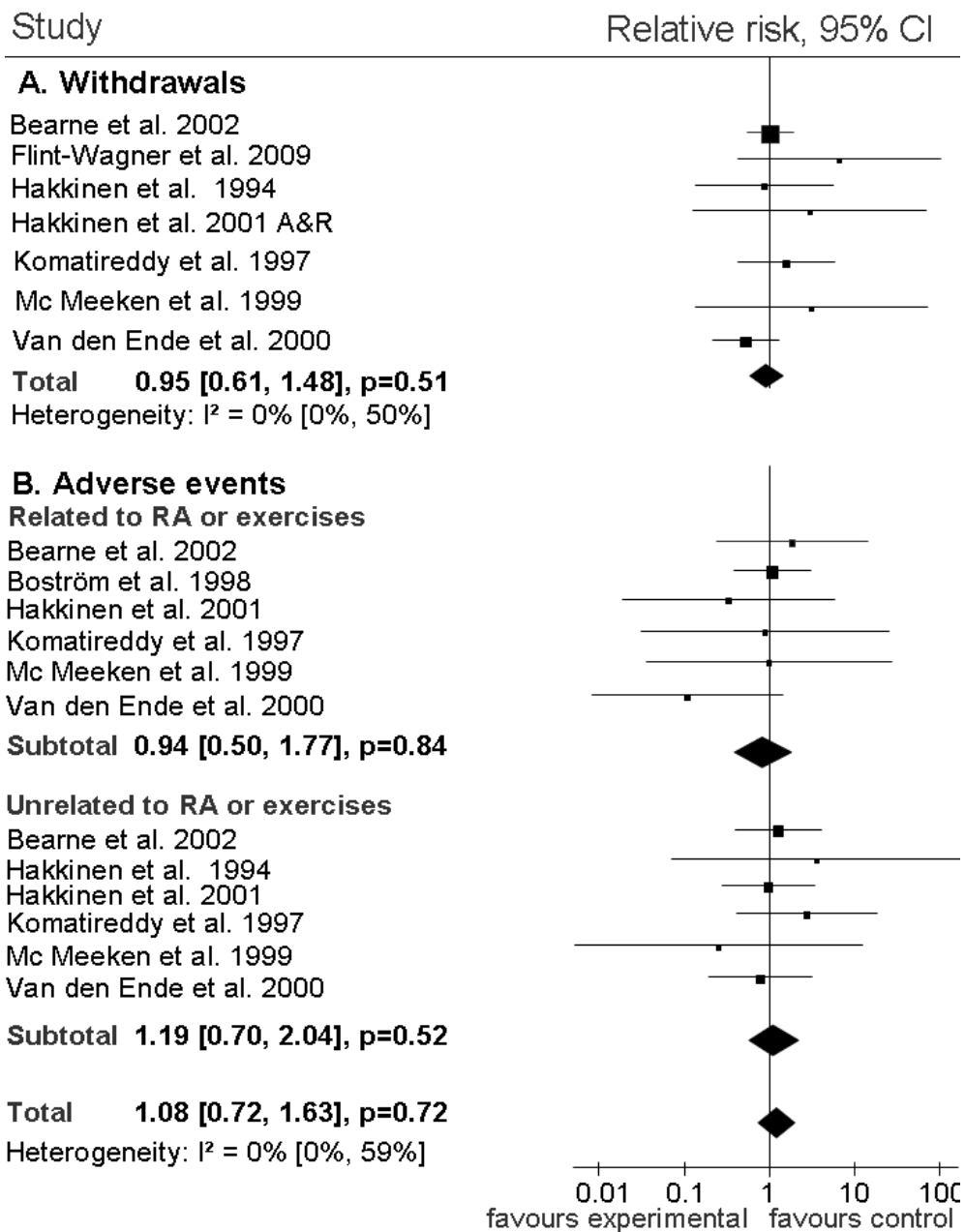
Data concerning disability assessed by the Health Assessment Questionnaire (HAQ) change (A), functional capacity assessed by the 50 feet walking test (B) and joint count (C) were pooled using inverse variance weighting and random effect methods. 95% CI=95% confidence interval.

**FIGURE 3. INFLUENCE OF RESISTANCE EXERCISES ON PAIN AND ERYTHROCYTE SEDIMENTATION RATE.**



Data concerning pain assessed by the Visual analogue scale (**A**) and erythrocyte sedimentation rate (ESR) at one hour (**B**) were pooled using inverse variance weighting and random effect methods. 95% CI=95% confidence interval.

**FIGURE 4. SAFETY OF RESISTANCE EXERCISES.**



Data concerning withdrawals (A) and adverse events (B) were pooled using inverse variance weighting and random effect methods. 95% CI=95% confidence interval.

## DISCUSSION

Les patients atteints de polyarthrite rhumatoïde ont une activité physique particulièrement faible [75], à l'origine d'une amyotrophie et d'un déconditionnement. Notre étude suggère que l'entraînement aérobie et le renforcement musculaire sont bien tolérés et permettent d'améliorer la plupart des critères d'évaluation de la PR.

Au delà de l'effet positif de la pratique d'exercices physiques sur la thymie du patient [37-39], il existe d'autres explications physiopathologiques aux bénéfices constatés dans notre étude. Edmonds et al. [40] ont proposé que les phénomènes d'ischémie-reperfusion au cours de l'exercice étaient comparables à une « auto-synovectomie » par diminution de vascularisation du pannus. De plus, il est probable que la pratique sportive ait une activité anti-inflammatoire intrinsèque par une modulation du réseau cytokinique avec une augmentation de médiateurs anti-inflammatoires comme l'interleukine 10 (IL-10) et l'IL-1Ra [41] contemporaine d'une production de cytokines pro-inflammatoires comme l'IL-6 [42]. En outre, l'exercice physique a un effet anabolique sur le muscle, notamment par activation de la voie Akt/mTOR [43] et par une production locale de facteurs de croissance tels que l'Insuline Growth Factor IGF-1 [44]. Enfin l'effet de l'exercice physique est probablement en partie attribuable à la diminution du volume du tissu adipeux, source majeure d'IL-6 [45, 46].

Certaines limitations doivent être prises en compte dans l'analyse de nos résultats. Tout d'abord, nous avons pu confirmer la faiblesse méthodologique des études que nous le suggérons dans une précédente revue [47]. Bien que la méta-analyse d'essais randomisés constitue le plus haut niveau de preuve scientifique en recherche clinique [48, 49], la mauvaise qualité méthodologique des études incluses dans nos méta-analyses limite la portée des résultats. Contrairement aux études de traitements pharmacologiques, il est difficile de respecter l'insu de l'intervention dans les travaux évaluant l'intérêt de l'activité physique. De plus, il existe des limitations métrologiques inhérentes aux études interventionnelles non pharmacologiques. En effet, la plupart des critères d'évaluation ont été mis au point pour la recherche clinique médicamenteuse et ne s'appliquent pas correctement aux interventions non pharmacologiques comme l'exercice physique [50, 51]. Le HAQ, par exemple, évalue surtout la fonction des membres supérieures des patients

atteints de PR et ne semble pas très sensible au changement au cours de l'exercice physique [52]. De plus, les évènements indésirables sont souvent mal décrits surestimant probablement la tolérance des patients à l'exercice physique [51]. Une meilleure définition *a priori* des effets adverses à analyser devrait permettre une amélioration substantielle de leur description [53] dans les futures études. Enfin peu d'études intègrent dans leur entraînement physique les recommandations de l'American College of Sport Medicine [54] : 20-60 min d'exercice aérobie 3-5 fois par semaine à 55-90% de la fréquence théorique maximale ; 8-12 séries de musculation 2-3 fois par semaine. Notre étude [35] confirme que l'entraînement pratiqué dans ces conditions est plus profitable qu'un entraînement moins intensif [55]. Il semble donc important de proposer un entraînement physique supervisé permettant d'améliorer la compliance et d'adapter l'intensité pour augmenter le bénéfice des exercices. Il est également probable que les exercices supervisés en groupe augmentent la motivation des patients, qui semble un facteur essentiel de la réussite d'un programme d'exercice physique [56].

Plusieurs questions importantes, hors du cadre de notre étude, n'ont pas pu être abordées. Tout d'abord nous n'avons pas clairement pu déterminer à quel type de patient l'intervention était la plus profitable. Notre analyse de sous-groupes suggère que l'exercice aérobie améliore d'autant plus la qualité vie que la maladie évolue depuis peu alors que les propriétés antalgiques de l'exercice aérobie semblent plus importantes dans la PR établie. En ce qui concerne le renforcement musculaire, nous n'avons pas détecté de critère démographique modifiant l'effet de l'entraînement car les populations des essais randomisés, sélectionnées sur des critères d'inclusions très semblables, étaient trop homogènes. Nous manquons de données pour les populations exclues des essais randomisés comme les patients âgés ou poly-pathologiques. En effet, une seule étude incluait des patients de plus de 65 ans [57]. Il est donc difficile d'extrapoler nos résultats aux patients de cette tranche d'âge, qui sont le plus à risque de fractures. L'amélioration de la fonction neuromusculaire et du risque de chute ont été suggéré dans la population générale [58-60], mais pas chez les patients atteints de PR pour qui l'exercice ne semble pas modifier la densité minérale osseuse [61]. De plus, nous n'avons pas pu analyser les conséquences de l'entraînement sur la survenue d'évènements cardio-vasculaires qui constituent la première cause de mortalité de la PR [62, 63]. Certaines études suggèrent

que l'inactivité corrèle avec la mortalité cardio-vasculaire [64, 65]. Dans la population générale, l'entraînement aérobic comme le renforcement musculaire permettent de réduire les facteurs de risque cardio-vasculaire [66, 67]. Des études devront être conduites pour confirmer l'effet cardio-protecteur de l'exercice physique dans la PR [68]. Par ailleurs, nous n'avons pas pu apprécier la rémanence du bénéfice du programme à l'issue de l'étude. Van den Ende et al. rapportent dans leur étude [69] que le programme d'exercice dynamique offre un effet d'une durée de quelques semaines alors que Hakkinen et al. [70] suggèrent un bénéfice à plus long terme. Il est encore incertain que les patients inclus aient poursuivi une activité physique régulière à l'issue de l'étude et que l'effet positif sur les critères d'évaluation persiste. Enfin, nous n'avons pas pu déterminer l'intérêt médico-économique de l'entraînement physique sur la prise en charge de patients atteints de PR. Les nouveaux traitements ciblés de la polyarthrite entraînent une dépense de santé conséquente de 16000 à 20000 € / an alors qu'un traitement de fond conventionnel est 5 à 7 fois moins important [71]. Ainsi le coût total de la maladie (coûts directs plus indirects) moyen par patient varie de 3072 à 49786 € / an [72]. Il est possible que l'exercice physique puisse réduire les dépenses liées aux biothérapies en abaissant l'indice de masse corporelle [73]. Il est également probable que l'entraînement diminue le coût lié aux complications cardio-vasculaires [68], aux chutes et aux fractures osseuses [74].

Les patients souffrant de PR sont volontaires pour participer à ces types d'intervention mais regrettent la mauvaise maîtrise de la prescription d'exercices par le corps médical [76], et souhaitent une meilleure information sur les risques et les bénéfices attendus ainsi que sur les types d'exercices devant être pratiqués. Il est donc capital que les médecins soient mieux informés sur l'efficacité et la tolérance de l'entraînement aérobic et du renforcement musculaire dans cette pathologie. Enfin, il semble important de conduire de nouvelles études afin de déterminer l'impact de l'exercice sur d'autres critères d'évaluations pertinents comme la survenue de chutes, de fractures ou d'évènements cardio-vasculaires et de déterminer à quels patients l'entraînement est le plus profitable. Sur un plan fondamental, il serait intéressant de mieux cerner les voies physiopathologiques par lesquelles l'entraînement exerce son effet bénéfique dans la PR afin de le proposer comme une intervention synergique avec le traitement de fond.

Thèse soutenue par : Athan BAILLET

**TITRE :** Intérêt de l'activité physique aérobie et du renforcement musculaire dans la polyarthrite rhumatoïde : analyses systématiques de la littérature et méta-analyses d'essais randomisés contrôlés.

**CONCLUSION :** La méta-analyse des 14 essais randomisés contrôlés, soit 1040 patients atteints de polyarthrite rhumatoïde, comparant une prise en charge classique à un entraînement aérobie a suggéré que ce type d'exercice améliore significativement la qualité de vie, la fonction, la douleur et l'évolution structurale avec une supériorité des programmes où les exercices été supervisés. De même, la méta-analyse de 10 essais randomisés contrôlés, soit 547 patients, montrait que le renforcement musculaire augmente significativement la force musculaire isométrique, isocinétique et de préhension ainsi que la fonction, le nombre d'articulations douloureuses ou gonflées et la vitesse de marche. De manière surprenante la vitesse de sédimentation était diminuée chez les patients ayant bénéficiés du renforcement musculaire.

La tolérance des deux types d'entraînement semblait bonne car on ne notait pas de majoration du nombre d'effets indésirables ou de patients abandonnant l'étude dans le groupe bénéficiant d'exercices par rapport au groupe contrôle.

Bien que notre étude ait montré l'intérêt de l'entraînement physique avec une bonne tolérance pour les patients atteints de PR, la faible qualité méthodologique des essais randomisés contrôlés inclus dans ces méta-analyses doit inciter la réalisation de nouvelles études pour clairement définir chez quels patients souffrant de polyarthrite rhumatoïde ce type d'intervention est le plus pertinent.

**VU ET PERMIS D'IMPRIMER**

Grenoble, le 27/6/2011

**LE DOYEN**



**LE PRESIDENT DE THESE**

**Pr. R. JUVIN**

A handwritten signature in black ink, corresponding to the name Pr. R. JUVIN.

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**ANNEXE 1 :**

**A dynamic exercise programme to improve patients' disability in rheumatoid arthritis: a prospective randomized controlled trial.**

**Baillet A, Payraud E, Niderprim VA, Nissen MJ, Allenet B, François P, Grange L,  
Casez P, Juvin R, Gaudin P.**

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# A dynamic exercise programme to improve patients' disability in rheumatoid arthritis: a prospective randomized controlled trial

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**Objective.** To evaluate the functional, clinical, radiological and quality of life outcomes of a 4-week dynamic exercise programme (DEP) in RA.

**Methods.** Patients matched on the principal medico-social parameters were randomly assigned to either the DEP or the conventional joint rehabilitation group. Primary end point for judging effectiveness was functional status assessed by HAQ. Secondary outcomes included Nottingham Health Profile (NHP), Arthritis Impact Measurement Scale 2—Short Form (AIMS2-SF) and radiological worsening measured by Simple Narrowing Erosion Score (SENS). Clinical evaluation consisted of disease activity score (DAS 28), cycling aerobic fitness and dexterity. Dexterity was measured using Sequential Occupational Dexterity Assessment (SODA) and Duruoz Hand Index (DHI). Data were collected at baseline, 1, 6 and 12 months.

**Results.** Fifty patients were enrolled. HAQ improved throughout the length of the trial in the DEP group. This improvement was greater in DEP than in the standard joint rehabilitation group at 1 month (−0.2 vs no variation from baseline,  $P=0.04$ ), but not at 6 months (−0.2 vs −0.1 in control group,  $P=0.25$ ) or 12 months (−0.1 vs no variation in control group,  $P=0.51$ ). DEP improved NHP (−23 vs +7% in control group,  $P=0.01$ ) and aerobic fitness (+0.3 vs +0.1 km per 5 min in control group,  $P=0.02$ ) at 1 month but the progress was not statistically significant thereafter. DEP also improved DHI, SODA, DAS 28 and AIMS2-SF, although not significantly.

**Conclusion.** DEP was effective on functional status assessed by HAQ, quality of life and aerobic fitness at 1 month.

**KEY WORDS:** RA, Rehabilitation, Exercise therapy, Dynamic exercise programme.

## Introduction

RA is the most common inflammatory arthritis and affects roughly 0.4% of the Caucasian population [1]. The mechanisms of synovial inflammation remain unclear but often lead to progressive joint destruction and deformation. The subsequent impairment in range of motion, muscle strength, endurance and aerobic fitness adds up to serious loss of function, work disability, dependency, impaired social and family function, reduced quality of life or low self-esteem [2]. The impact of the disease in the medico-economic domain is critical and joint rehabilitation constitutes the cornerstone of physical therapy [2, 3]. During flares, pain obviously requires rest and gentle, passive, non-weight-bearing exercise. Dynamic exercise programmes (DEPs), which have been developed in other diseases such as chronic airway obstruction or coronary heart disease [4, 5] in order to reduce the patient's handicap, are now being used for the rehabilitation of RA patients. Although there is no standardized design of DEP for patients suffering from RA, most of the programmes follow the recommendations issued by the American College of Sports Medicine for healthy individuals [6]. Exercise must lead to a 60% increase of predicted maximal heart rate over 20 min, at least twice a week to exhibit clinical positive effects (improvement of muscular strength and aerobic capacity). The scientific evaluation of DEP in this disease has led to conflicting results. In a recent literature review [7] of the nine randomized controlled studies evaluating DEP in RA [8–16], we have underlined the methodological bias limiting the interpretation of previous studies. These publications provide several lines of

evidence for improvement in aerobic capacity and muscle strength but conclusions concerning functional ability, physical capacity, quality of life and structural damages could not be drawn. Therefore, we designed this single-blinded RCT in order to determine whether a standardized DEP could provide beneficial effects with regards to these above-mentioned parameters.

## Patients and methods

### Patients

In April 2004, patients registered in the various rheumatology departments of the Grenoble University Teaching Hospital who fulfilled the 1987 modified ACR criteria for RA [17] were screened for inclusion in the study as well as for demographic and disease-related parameters (Table 1). Every patient at inclusion was being treated with a DMARD. All participants gave written consent, prior to inclusion, according to the Declaration of Helsinki. Local medical ethics committee gave the ethical approval for this study (CCPPRB Grenoble II, 11 December 2002). An ECG was performed for every patient and a consultation with a cardiologist was scheduled for all patients older than 45 years, with positive cardiovascular risk factors or with an abnormal ECG. Exclusion criteria were: treatment with >10 mg glucocorticoid per day, no or unstable DMARD regimen, disease activity score 28 (DAS 28) variation >1.2 in the past 3 months, an age <18 or >70 years and global functional status in RA class III or IV [18]. Patients unable to follow the educational programme or complete a questionnaire because of cognitive impairment, psychiatric disease or language difficulty were also excluded from this study. Inability to perform aerobic exercise or complete the 1-year follow-up because of health problems or socio-professional status also constituted exclusion criteria. Biological assessment at baseline included: complete blood count, ESR, CRP, RF, serum glutamic oxaloacetic transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), creatinine, serum calcium and ALP.

A sample size of 38 patients in the DEP group and 76 patients in the control group was required to detect an HAQ difference of 0.25 between both groups with 90% power and a significance level

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of 0.05. To compensate for an expected 20% dropout, we planned to include 48 patients in the DEP group and 96 patients in the control group. Unfortunately, we were not able to enrol enough patients and the sample size was limited to 50 patients, based on previous studies [9, 12–15].

### Randomization procedure

The randomization process was carried out by an independent physician who was not responsible for recruiting the patients, at a central location. Patients were randomly assigned to either a DEP or a conventional joint rehabilitation by means of sealed and opaque envelopes. Study observers remained unaware of study-group assignments throughout the trial.

### Interventions

The DEP was consistent with the 1990 recommendations of the American College of Sports Medicine [6]. Three or four members of the medical staff (rheumatologist, physiotherapist or occupational therapist) took part in each session for 5 h a day during a 4-week period (Table 2).

During the first week, following a multidisciplinary meeting, knowledge of the disease and physical capacity were evaluated for each participant in order to design an individualized exercise programme. The second week of occupational therapy input focused on the influence of RA on daily activities. The occupational therapy programme in the third week included skill exercises and daily activities with increasing intensity (endurance and exercises against resistance). During the fourth week the exercises focused on office tasks.

The training programme was designed to improve muscle strength, flexibility, endurance and balance. Exercises for the

upper and lower limbs were performed five times a week in a gymnasium (cycling, running or resisting pulley cord, 45 min/day) and in a hydrotherapy pool (60 min/day). During cycling, the heart rate was kept at 60–80% of the predicted maximal heart rate ( $220 - \text{age}$ ). Resistance and intensity of exercise were designed after individual evaluation of each patient and modified according to pain and fatigue. Regular breaks and relaxation sessions were scheduled in order to improve pain tolerance and self-esteem. Each session was preceded by a 'warm-up' and followed by a 'cool-down'. The patients were asked to keep a diary of their daily training.

Patients in the control group received a multidisciplinary programme with a rheumatologist, a physiotherapist, an occupational therapist, a social worker, a pharmacist and a psychologist. This 3-day intervention (~20 h) was designed to improve knowledge about disease pathogenesis, RA management and joint protection. Each training group consisted of four or five patients accompanied by relatives or friends. The following fields were covered during lectures: mechanisms of RA, benefits and limitations of drug therapy, psychological impact of the disease (first day); dietetic counselling (second day); and use of splints, surgical perspectives and counselling on activities of daily living or work (third day). Patients benefited from a hydrotherapy session (for 45 min at 35°C) on the first day and relaxation exercises (45 min) on the second day. Physical exercises (45 min/day) aimed at preventing muscles from atrophy and tension. Each day ended with an individual discussion where disease-related problems were verbalized and possible solutions were offered. The training was completed by means of educational films or activities covering the aspects of the programme.

To standardize the delivery of interventions, written forms detailed the coaching process based on the French Rheumatology Society recommendations, and patients received an educational booklet. Three physiotherapists were trained to carry out the physical intervention.

### Primary outcome

The primary outcome was the functional status evaluated by HAQ [19] at 1, 6 and 12 months. HAQ, whose total score ranges from 0 (no functional limitation) to 3 (dramatical functional impairment), was selected as the primary outcome measure because of its ability to measure the function of large and small joints by the patients' multidimensional ability to perform activities of daily living. Its validity in assessing disability in RA is well established.

TABLE 1. Demographic, clinical and radiological characteristic of the population

Characteristics	DEP group (n=25)	Control group (n=23)
Age, mean $\pm$ s.d., years	51.6 $\pm$ 8.3	56.3 $\pm$ 12.8
Female, n (%)	21 (84.0)	18 (78.3)
Disease duration, mean $\pm$ s.d.	10.5 $\pm$ 8.0	11.7 $\pm$ 6.2
Morning stiffness, mean $\pm$ s.d.	59.8 $\pm$ 75.1	55.7 $\pm$ 97.4
Completers, n (%)	25 (100)	20 (80)
Professional status		
Full-time job, n (%)	6 (24.0)	5 (21.7)
Part-time job, n (%)	6 (24.0)	3 (13.0)
Unemployed, n (%)	0 (0.0)	1 (4.3)
Disabled, n (%)	5 (20.0)	1 (4.3)
Retired, n (%)	4 (16.0)	10 (43.5)
Education level		
Last year of study, mean $\pm$ s.d.	22.4 $\pm$ 16.9	20.2 $\pm$ 7.3
University training, n (%)	8 (32.0)	7 (30.4)
RA global functional ACR Index <sup>a</sup>		
ACR I, n (%)	7 (28.0)	11 (47.8)
ACR II, n (%)	16 (64.0)	12 (52.2)
DAS 28 (0.14–9.3) <sup>a</sup> , mean $\pm$ s.d.	4.9 $\pm$ 1.4	4.0 $\pm$ 1.7
<3.2	4 (16.0)	7 (30.4)
3.2–5.1	11 (44.0)	8 (34.8)
>5.1	10 (40.0)	6 (26.1)
VAS (0–100), mean $\pm$ s.d.	34.4 $\pm$ 23.0	31.4 $\pm$ 24.3
Functional status		
HAQ (0–3), mean $\pm$ s.d.	0.9 $\pm$ 0.6	0.7 $\pm$ 0.5
Quality of life		
NHP (0–600), mean $\pm$ s.d.	220.7 $\pm$ 122.4	201.6 $\pm$ 129.6
AIMS2-SF (0–60), mean $\pm$ s.d.	21.2 $\pm$ 5.6	19.6 $\pm$ 4.9
Dexterity and aerobic fitness		
DHI (0–90) mean $\pm$ s.d.	28.8 $\pm$ 21.8	16.0 $\pm$ 12.2
SODA (0–108) mean $\pm$ s.d.	60.0 $\pm$ 12.6	63.6 $\pm$ 6.9
Home bicycle, mean $\pm$ s.d. <sup>b</sup> , km	1.1 $\pm$ 0.4	1.2 $\pm$ 0.2
Treatment <sup>c</sup>		
Biotherapy (anti-TNF- $\alpha$ or IL-1 $\beta$ ), n (%)	14 (56.0)	11 (48.0)
Glucocorticoid, means (range), mg/day	6 (0–10)	5 (0–10)
SENS (0–86), median (IQR) <sup>d</sup>	$\pm$ 3 (0–13)	$\pm$ 5 (2–20)

<sup>a</sup>Two missing values. <sup>b</sup>Twenty missing values. <sup>c</sup>All patients were currently treated with a DMARD. <sup>d</sup>Eight missing values.

TABLE 2. Content of the DEP: role of occupational therapists and physiotherapists

	Occupational therapy	Physiotherapy
First week	Presentation of the multidisciplinary team Patient's individual expectations Evaluation of the patient's knowledge of the disease and physical capacity in order to design specific programme	Hydrotherapy Pain relief Improvement in range of motion Muscle strengthening
	Explanation of the disease and its consequences Occupational therapy advices Evaluation of the patient's splint and construction of rest splint Dexterity exercises without resistance	Fitness programme (gym, bicycle) Stretching Relaxation Educational booklet
Second week	Exercises concerning usual tasks	
Third week	Splint construction and evaluation Exercises concerning dexterity exercises Increasing resistance and range of motion in dexterity exercises	
Fourth week	Evaluation of disease-related difficulties during usual office tasks Splint construction	

### Secondary outcomes

Secondary outcomes included quality of life, functional, clinical, radiological, therapeutic and biological modifications in both groups. The French version of the Arthritis Impact Score 2—Short Form (AIMS2-SF) [20], is a specific questionnaire to assess quality of life in RA patients. AIMS2-SF was not converted to a score of 0–10, but was expressed on a scale from 0 to 60. Nottingham Health Profile (NHP) is a 38-item generic health-related quality of life measure (range 0–600, higher score for greater health problems) [21]. Patient dexterity was evaluated by occupational therapists using Sequential Occupational Dexterity Assessment (SODA; [22]) or self-reported by patients using Duruoz Hand Index (DHI) [23]. SODA consists of 12 standardized tasks evaluated by occupational therapists and ranges from 0 (inability to perform tasks) to 108 (no difficulty in performing tasks). The purpose of DHI (range 0—excellent dexterity to 90—poor dexterity) was to measure hand ability while performing personal hygiene, office tasks and other general activities. Simple Erosions Narrowing Score (SENS; range 0–86; [24]) evaluates erosions in 32 joints in the hands, 12 in the feet and joint space narrowing in 30 and 12 joints, respectively. The total SENS score was assessed by a single radiologist unaware of the group assignment. Disease activity was determined using disease activity score (DAS 28; range 0.14–9.3; [25]). A 28-joint count for swelling and tenderness was assessed by a rheumatologist unaware of the treatment allocation. Patients rated their general health on a 100-mm visual analogue scale (VAS). DAS 28 was calculated using the three previously mentioned parameters and ESR. Aerobic fitness was measured on an exercise bike as the distance covered in 5 min [26]. Since the primary outcome (HAQ score) and some of the secondary outcomes (DHI and SODA) are dependant on the upper limb function, we wanted to avoid a difference in dexterity between DEP and control groups. Therefore, Roeder Manipulative Aptitude Test [27], five-handle position grip test [28], Grip and Pinch Strength test [29] were measured at baseline to avoid a potential confounder. The uses of oral and IA drugs as well as other medical devices were noted.

### Assessment of outcomes

Primary and secondary outcomes were evaluated at baseline, 1, 6 and 12 months, except for SENS which was evaluated at the

baseline and 12 months. Questionnaires were sent by mail to each patient every 3 months. Every clinical evaluation was performed by a physician unaware of the patients' group allocation.

### Statistical analysis

Measures with a Gaussian distribution were expressed as mean  $\pm$  s.d. and measures with a non-Gaussian distribution were expressed as the median and interquartile range (IQR; expressed as the net result of 75th percentile – 25th percentile). We confirmed with a Kolmogorov–Smirnov test that primary and secondary outcomes, except SENS, were normally distributed.

Statistical significance of the variation of these values from baseline between DEP and standard joint rehabilitation was determined using analysis of covariance (ANCOVA) [30]. *P*-values  $<0.05$  were considered statistically significant. The analyses were based on the intent to treat as initially assigned. All available data were used. Statistical analysis was performed using Stata 9.0 (Stata Corporation College Station, TX, USA).

## Results

### Baseline characteristics

Out of 827 patients eligible after screening, 440 were excluded because of exclusion criteria, 312 eligible participants refused the programme and 25 stopped the trial before the baseline visit because of personal reasons not included in the exclusion criteria or unwillingness to participate (infection, travel, etc.). Twenty-five patients were randomly assigned to DEP and 25 to standard joint rehabilitation. Two individuals refused to participate immediately after randomization (Fig. 1). The randomization procedure created two groups whose baseline demographic and disease-related parameters (clinical, functional, radiological and biological) were similar (Table 1) except for RA Global Functional ACR Index which was better in the standard joint rehabilitation group (28% ACR I in DEP vs 47.8% in control). Functional status, measured by HAQ, did not differ significantly between the two groups. Thirteen patients in the DEP group and 11 in the standard joint rehabilitation group were treated by either anti-IL-1 $\beta$  or anti-TNF- $\alpha$ ; five patients were taking glucocorticoids in the DEP group and nine in the standard joint rehabilitation group. No patients were lost to follow-up, but one subject was not assessed

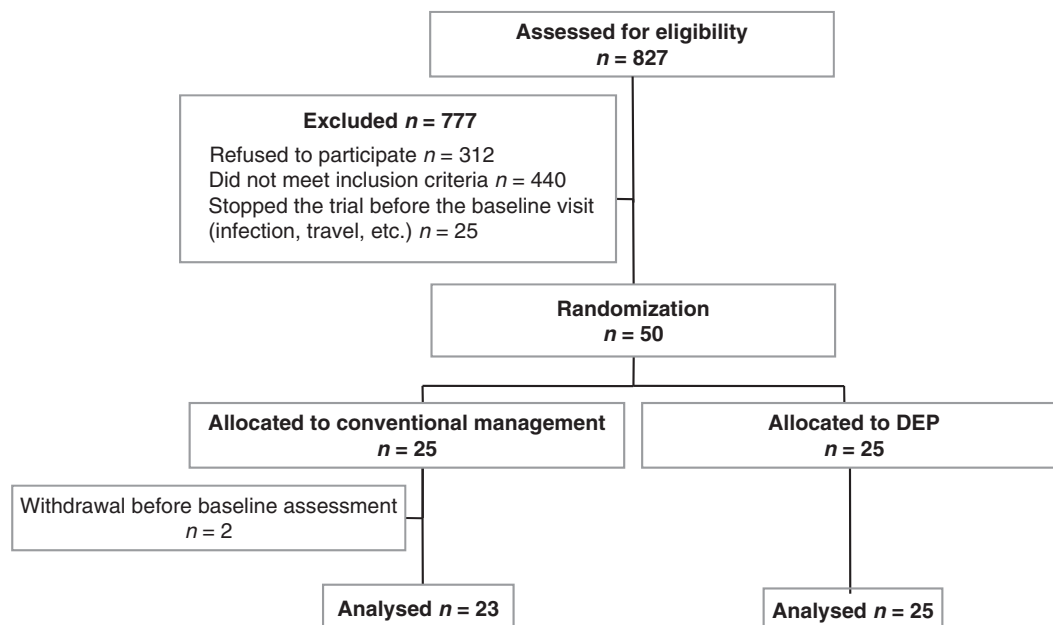


Fig. 1. Trial flowchart.

for NHP and AIMS2-SF at 1 month. Three patients were not assessed at 6 months and four patients were not assessed at 12 months (Tables 3 and 4).

### Primary end point

We observed an improvement in HAQ measurement throughout the length of the trial in DEP. This improvement was greater in DEP than in the standard joint rehabilitation group at 1 month (−22% vs no variation from baseline,  $P=0.04$ ). The variation in HAQ scores from baseline between the two groups did not reach statistical significance at 6 months (−22 vs −14%,  $P=0.25$ ) or 12 months (−11% vs no variation from baseline,  $P=0.51$ ) (Table 3). The change in HAQ score in the DEP group at 1 month and 6 months (−0.2) almost reached clinical significance [31].

### Secondary end points

In the DEP, all parameters globally improved during the trial. This change was most obvious after the first month compared with baseline (DAS 28: 3.8 vs 4.9; NHP: 170.2 vs 220.7; AIMS2-SF: 18.0 vs 21.2; DHI: 19.9 vs 28.8; SODA: 60.6 vs 60.0; and aerobic fitness: 1.4 vs 1.1 km, respectively). A variation of 0.6 points in DAS 28 assessment is commonly considered to be clinically meaningful [31]. NHP and AIMS2-SF scores are presented as a profile rather than overall score and the minimal detectable change or the minimal important change still needs to be assessed. Among the secondary end points, we demonstrated an increase in quality of life measured by NHP in DEP (−23 vs +7% in control,  $P=0.01$ ) but not AIMS2-SF (−15 vs +2% in controls,  $P=0.09$ ) at 1 month (Table 4). Improvement of aerobic fitness, measured on an exercise bike, was statistically better in the DEP group than in the standard joint rehabilitation group (+0.2 km in 5 min,  $P=0.02$ ), but no statistically functional superiority of DEP could be detected on DHI ( $P=0.35$ ) or SODA ( $P=0.30$ ) at 1 month (Table 4).

Although quality of life and disease activity demonstrated a positive trend at 6 and 12 months in comparison with baseline (Tables 3 and 4), the changes of DAS 28, NHP, AIMS2-SF, DHI and SODA were not statistically significant between groups. Although not statistically different from the control group, improvement in DHI at 1 month (from 28.8 to 19.9), 6 months (from 28.8 to 15.4) and 12 months (from 28.8 to 19.2) is higher than the minimal detectable change [32]. Aerobic fitness, measured on an exercise bike, improved with DEP but not with standard joint rehabilitation at 6 months (+18% vs no variation,  $P=0.20$ ) and at 12 months (+18 vs −8%,  $P=0.16$ ). The radiological evaluation did not demonstrate any difference between the two groups at 12 months. We did not observe any significant worsening in SENS assessment in DEP in comparison with control.

### Safety and compliance

No adverse effects were seen in either group. Two patients in the DEP and four patients in the standard joint rehabilitation group switched to another anti-TNF- $\alpha$  treatment. There was no difference in disease activity or inflammatory parameters (DAS 28, VAS, ESR and CRP) between the groups during the trial. There were no dropouts from either group.

### Discussion

Previous studies supported evidence for improvement of aerobic fitness [9–11, 16, 33] and muscle strength [11, 33–37] after exercise interventions in RA. The specific effects of exercise on functional status evaluated by HAQ or quality of life remain unclear [38]. This randomized controlled single-blind study achieved its primary end point, i.e. the reduction of HAQ and demonstrated

TABLE 3. Primary outcome (HAQ) during follow-up

	DEP (N=25)			Control (N=23)			P-value*
	Mean	(s.d.)	Change from baseline (%)	Mean	(s.d.)	Change from baseline (%)	
HAQ 1 month	0.7	(0.6)	−22	0.7	(0.6)	0	0.04
HAQ 6 months <sup>a</sup>	0.7	(0.6)	−22	0.6	(0.6)	−14	0.25
HAQ 12 months <sup>b</sup>	0.8	(0.6)	−11	0.7	(0.5)	0	0.51

HAQ: 0—no disability to 3—great disability. <sup>a</sup>Three patients not assessed. <sup>b</sup>Four patients not assessed. \*P-values are determined using ANCOVA.

TABLE 4. Secondary outcomes (disease activity, disability, quality of life status, dexterity and aerobic fitness) during follow-up

	DEP (N=25)			Control (N=23)			P-value*
	Mean	(s.d.)	Change from baseline (%)	Mean	(s.d.)	Change from baseline (%)	
1 month							
DAS 28	3.8	(2.1)	−22	4.0	(1.6)	0	0.19
NHP <sup>a</sup>	170.2	(129.4)	−23	215.7	(149.6)	+7	0.01
AIMS2-SF <sup>a</sup>	18.0	(5.7)	−15	19.9	(7.1)	+2	0.09
DHI	19.9	(16.9)	−31	14.6	(15.9)	−9	0.35
SODA	60.6	(11.4)	+1	60.8	(11.1)	−4	0.30
Exercise bike (km/5 min)	1.4	(0.3)	+27	1.3	(0.2)	+8	0.02
6 months <sup>b</sup>							
DAS 28	4.1	(1.9)	−16	3.9	(2.1)	−3	0.96
NHP	192.5	(128.9)	−13	187.5	(163.9)	−7	0.46
AIMS2-SF	20.4	(6.3)	−4	20.1	(7.5)	+3	0.44
DHI	15.4	(13.9)	−47	11.8	(11.4)	−26	0.38
SODA	61.3	(10.8)	+2	60.8	(9.3)	−4	0.18
Exercise bike (km/5 min)	1.3	(0.3)	+18	1.2	(0.3)	0	0.20
12 months <sup>c</sup>							
DAS 28	4.5	(2.1)	−8	3.8	(1.8)	−5	0.39
NHP	198.5	(134.1)	−10	192.8	(130.2)	−4	0.43
AIMS2-SF	20.6	(7.5)	−3	19.5	(6.6)	−1	0.94
DHI	19.2	(17.9)	−33	13.3	(10.8)	−17	0.74
SODA	60.5	(9.4)	+1	60.3	(8.6)	−5	0.18
Exercise bike (km/5 min)	1.3	(0.2)	+18	1.1	(0.3)	−8	0.16

DAS 28: 0.14—no activity to 9.3—high activity; NHP: 0—good quality of life to 600—poor quality of life; AIMS2-SF: 0—good quality of life to 60—poor quality of life; DHI: 0—good dexterity to 90—poor dexterity; SODA: 0—poor dexterity to 108—good dexterity. <sup>a</sup>One missing value. <sup>b</sup>Three patients not assessed. <sup>c</sup>Four patients not assessed. \*P-values are determined using ANCOVA.

that a DEP provided better effects on quality of life (NHP) than conventional joint rehabilitation at 1 month.

Although our results are promising, some limitations must be considered. First, we did not record either patients' current level of physical activity or their recent experience with rehabilitation, which could influence the baseline test parameters and the subsequent change at the different end points. Patients' allocation was randomly performed but we cannot be sure that these potential confounders were equally distributed in DEP and control groups. Secondly, we evaluated compliance as the number of completers but not as the percentage of the maximum possibly attended sessions, which appears to be a more precise measurement of compliance. There was excellent compliance in our study with no withdrawals from either group. This result is in concordance with previous studies describing at least 70% completion in the intervention groups. As both groups in our study underwent different types of interventions (intensive aerobic exercise vs education and classical rehabilitation), a discrepancy in compliance is unlikely to explain the good result in the DEP group. Most previous studies reported compliance as the number of completers. Only a few studies, mostly long-term intervention trials comparing similar interventions, reported compliance as a percentage of the maximum possibly attended sessions. Among the 32 RCTs comparing an aerobic exercise programme to less

intensive rehabilitation in RA, only six trials (19%), whose intervention lasted at least 12 weeks, evaluated this parameter. In a home-based physical activity intervention, Van den Berg *et al.* [39] reported that 34% of patients were physically active in the intervention group. Thirdly, the small number of patients included in this study is likely to be insufficient to detect a statistical difference in the primary and secondary outcomes between both groups at 6 and 12 months. Finally, missing data could yield biased results in our intent to treat statistical analysis. Contrary to the numerous missing values in baseline home-bicycle sprint assessment that might limit the conclusion of a DEP effect on physical capacity, only seven HAQ measurements (4%) were missing, which is unlikely to constitute an attrition bias.

Our findings confirm the results of earlier studies [36, 40], which reported a lower HAQ in an exercise intervention group, contrasting with most of the previous studies that failed to detect any statistical difference in HAQ variation between interventional and conventional joint rehabilitation [11, 14, 41, 42]. Two trials [8, 15] were able to show that DEP provides better functional results than control. In these studies—the McMaster Toronto Arthritis Patient Preference Questionnaire (MACTAR) and SF-36—two quality of life questionnaires containing functional ability items were used to assess functional impairment. To assess this last parameter we selected the widely used HAQ questionnaire that appears to be more specific for the functional ability assessment in RA. This index depends more on disease activity and pain than limb function and is more sensitive to detect change in function of the upper limbs than the lower limbs [43]. It is probably more appropriate in pharmacological trials than in physical intervention trials and might therefore be less sensitive to changes in groups with a score below 1.00 [44]. Thus, by using HAQ we possibly missed small but clinically relevant improvement of lower limb disability, and the lack of significant improvement of HAQ after 1 month may reflect an inability of this index to detect the effects of DEP rather than a failure of DEP to improve patients' functional status [38, 43]. Similarly, as Stenström *et al.* [45] reported an improvement of NHP score after dynamic training in patients with inflammatory rheumatic diseases, we have shown that the intervention group displayed improved health-related quality of life with NHP being statistically higher in DEP than in the control group as early as the first month. After the first month, the exercises were home-based and self-administered. The patients could therefore no longer benefit from the group dynamic, explaining the reduction in effect of DEP on NHP and other questionnaires concerning quality of life with time. Therefore, we cannot exclude that the enthusiasm of patients and the health professionals involved in this short-term intervention trial influenced the outcome.

The cost effectiveness of DEPs compared with usual management could not be evaluated because of missing data on self-reported questionnaires. We were unable to quantify the impact of a DEP on work and on the consumption of medical and paramedical resources, in order to determine whether the intervention programme, which is more expensive (10 000 euros for a DEP vs 1500 euros for usual management), was economically relevant.

The radiological evaluation did not demonstrate any deleterious effects of the DEP, which is consistent with two previous studies [8, 14]. Although our study was underpowered to prove any benefit in the DEP group in terms of joint damage, a previous study has reported less erosive change in patients treated with a DEP compared with usual care physical therapy [46]. Given that both study groups displayed differences of disease duration and baseline joint damage, no solid conclusions could be drawn on the protective effect of exercise on joints from this study [7]. Molecular mechanisms are still unclear but some cytokines such as insulin growth factor 1 (IGF1) are up-regulated in DEP [47].

Our study, based on stringent methodological procedure, provides evidence for quality of life improvement following DEP. We have confirmed that this type of intervention has

positive consequences on aerobic fitness with excellent compliance.

### Rheumatology key messages

- A DEP in RA improves HAQ at 1 month but not subsequently.
- DEP provides beneficial effects on quality of life.

### Acknowledgement

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*Disclosure statement:* The authors have declared no conflicts of interest.

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**ANNEXE 2 :**

**Résultats supplémentaires publiés en ligne pour l'article 1 :**

**Baillet A, Zeboulon N, Gossec L, Combescure C, Bodin AL, Juvin R, Dougados M,  
Gaudin P.**

**Efficacy of cardiorespiratory aerobic exercise in rheumatoid arthritis :**

**meta-analysis of randomized controlled trials**

**Arthritis Care Res (Hoboken) 2010;62:984-92**

**SUPPLEMENTARY TABLE 1: REFERENCES OF OUTCOME MEASURES**

Health-related parameter	Outcome measure	Abbreviation	Ref.
Quality of life	Nottingham Health Profile	NHP	(1)
	Rheumatoid Arthritis Quality of Life	RAQoL	(2)
	Physical component of the 36-item short-form health survey	SF-36 Phys	(3)
	Original Arthritis Impact Measurement Scales Health Status Questionnaire	AIMS	(4)
	McMaster Toronto Arthritis	MACTAR	(5)
Function	Health Assessment Questionnaire	HAQ	(6)
Disease activity	Disease activity score	DAS 28	(7)
Joint count	Ritchie index	Ritchie	(8)
Radiological evaluation	Larsen's method	Larsen	(9)

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**SUPPLEMENTARY TABLE 2: DEMOGRAPHIC CHARACTERISTICS IN 14 RANDOMIZED CONTROLLED TRIALS**

	Intervention group								Control group							
	Age, yr mean (SD)	RA onset, yr mean (SD)	n	Women %	Completers %	RF+ %	DMARD %	Age, yr mean (SD)	RA onset, yr mean (SD)	n	Women %	Completers %	RF+ %	DMARD %		
Bilberg [77] <sup>1</sup>	49.0 (~10)	2.6 (1.3)	22	nr	91.7	nr	81.8	46.0 (~14.7)	2.9 (1.4)	27	nr	85.2	nr	80.0		
Van den Berg [78] ¥ <sup>2</sup>	49.5 (9.6)	7.6 (6.5)	82	75.6	93.9	64.6	90.2	49.8 (10.4)	5.5 (8.4)	78	76.9	96.2	59.0	89.7		
de Jong [79] ¥ <sup>2</sup>	54.0 (11.9)	5.0 (5.2)	150	79.3	90.7	71.3	74.0	53.5 (13.3)	7.5 (8.0)	150	78.7	96.7	70.7	78.0		
Westby [80]	56.4 (10.1)	13.4 (10.4)	14	100.0	71.4	nr	28.6	56.4 (10.8)	12.6 (10.7)	16	100.0	62.5	nr	18.8		
Van den Ende [69]	62.0 (13.0)	8.0 (8.0)	34	58.8	82.4	88.2	nr	58.0 (14.0)	7.0 (8.0)	30	66.7	66.7	63.3	60.0		
Melikoglu [81]	46.2 (8.3)	6.7 (6.3)	20	100.0	95.0	nr	nr	50.3 (9.7)	6.0 (5.7)	20	100.0	85.0	nr	nr		
Hansen [28] ¥ <sup>2</sup>	55.0 (10.4)	1.2 (3.6)	15	80.0	93.3	73.3	73.3	51.0 (8.2)	8.0 (4.4)	15	66.7	86.7	93.3	73.3		
	52.0 (8.9)	1.0 (3.6)	15	46.7	93.3	86.7	73.3									
	51.0 (10.4)	1.2 (3.7)	15	60.0	73.3	86.7	60.0									
	54.0 (8.9)	1.0 (5.9)	15	73.3	86.7	73.3	nr									
Harkcom [82]	51.5 (3.1)	12.2 (8.7)	5	100.0	80.0	nr	nr	45.1 (19.3)	8.8 (10.1)	6	100.0	100.0	nr	nr		
	47.3 (14.5)	10.6 (5.5)	4	100.0	75.0	nr	nr									
	44.0 (18.3)	5.6 (3.7)	5	100.0	80.0	nr	nr									
Van den Ende [30]	51.1 (9.5)	11.5 (8.4)	25	52.0	60.0	84.0	nr	56.1 (10.9)	11.2 (9.8)	25	72.0	nr	76.0	nr		
	47.7 (13.6)	8.4 (5.8)	25	64.0	80.0	80.0	nr									
	53.1 (12.1)	8.6 (7.1)	25	64.0	92.0	76.0	nr									
Baillet [31]	51.3 (8.3)	10.5 (8.3)	25	100.0	84.0	nr	nr	56.3 (12.8)	11.7 (1.5)	23	78.3	87.0	nr	nr		
Neuberger [83]	nr	nr	84	nr	81.0	nr	nr	nr	nr	75	nr	97.3	nr	nr		
	nr	nr	89	nr	88.8	nr	nr									
Nordemar [84]	56.0 (9.0)	16.0 (7.0)	23	85.2	85.2	nr	56.5	58.0 (10.0)	14.0 (7.0)	23	82.6	92.0	nr	60.9		
Noreau [38]	49.3 (13.0)	8.1 (8.2)	19	63.2	100.0	nr	68.4	49.4 (11.9)	11.2 (2.1)	10	80.0	100.0	nr	60.0		
Lyngberg [57]	65.0 (10.8)	12.4 (11.1)	12	nr	83.3	nr	50.0	68.0 (7.2)	11.7 (10.1)	12	nr	nr	nr	16.7		
<b>Overall</b>	<b>52.8</b>	<b>7.8</b>		<b>76.9</b>	<b>86.8</b>	<b>77.5</b>	<b>70.6</b>	<b>54.5</b>	<b>9.3</b>		<b>80.2</b>	<b>87.2</b>	<b>75.9</b>	<b>66.2</b>		

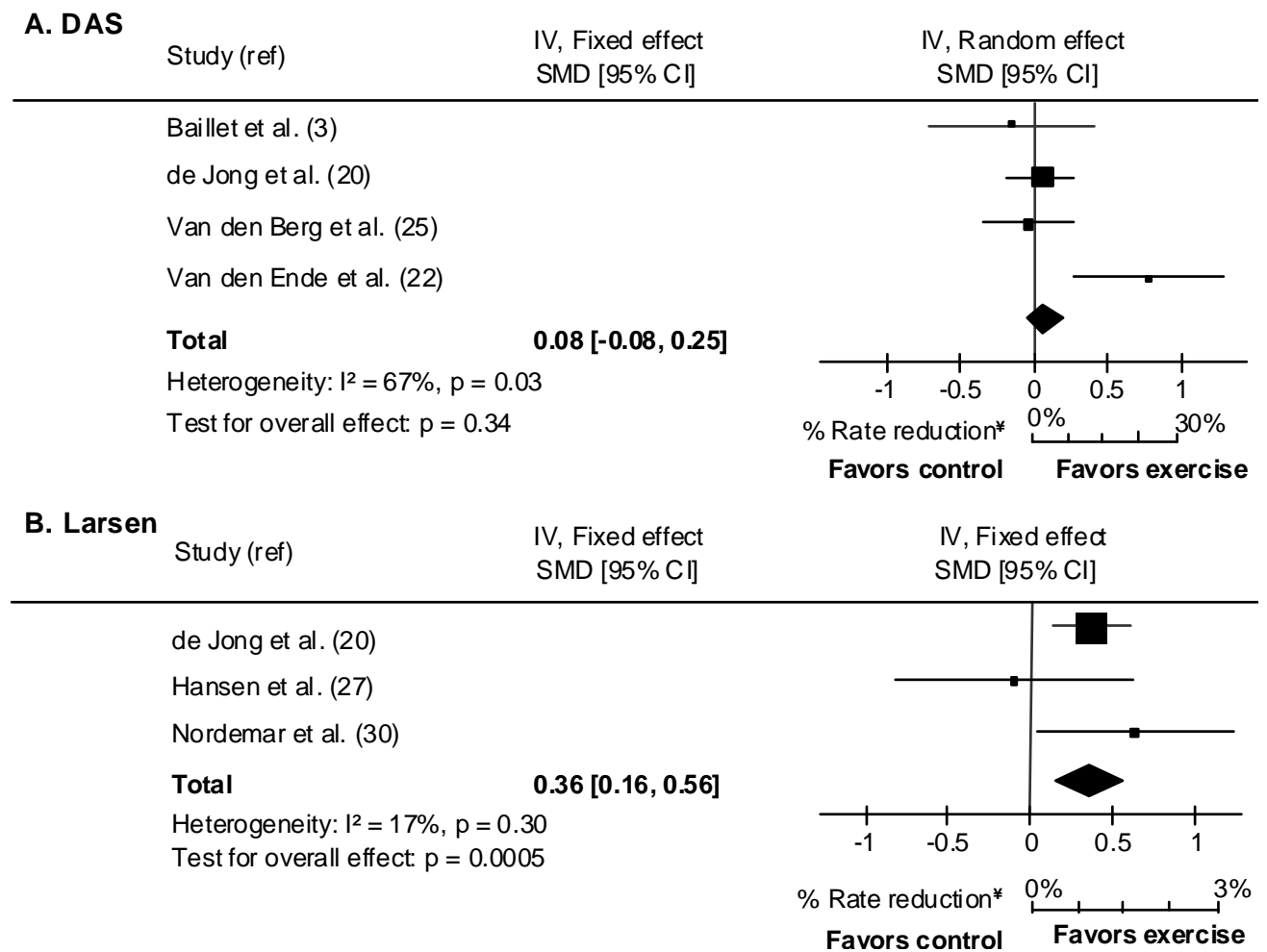
Value dispersion is standard deviation (SD) as given in articles or inferred from range<sup>1</sup>, interquartile range<sup>2</sup>. Results are means except ¥, where results are medians. RA = rheumatoid arthritis; RF+ = rheumatoid factor positive; DMARD = disease-modifying antirheumatic drugs; yr = years.

**SUPPLEMENTARY TABLE 3: EFFICACY OF CARDIORESPIRATORY AEROBIC EXERCISES IN 14 RANDOMIZED CONTROLLED TRIALS ON QUALITY OF LIFE, FUNCTION, PAIN, JOINT COUNT, AND RADIOLOGIC DAMAGES ACCORDING TO THE END POINT ASSESSMENTS**

	Quality of life <i>outcome</i>	≤3			~6			≥12			VAS			Larsen score			Joint count			
		mo			mo			mo			mo			mo			mo			
		mo			mo			mo			mo			mo			mo			
Bilberg [77]	<i>SF-36 phys</i>	+			ns	ns	ns													
Van den Berg [78]	<i>RAQol</i>	ns	ns	ns	+	+	+		ns	ns										
De Jong [79]	<i>MACTAR</i>				+			ns	ns			+					ns*			
Westby [80]								ns												ns
Van den Ende [69]					ns	ns			ns	ns		-/ns**	ns						S+TJC	
Melikoglu [81]					ns							+							S+TJC	ns
Hansen [28]								ns						ns					Ritchie	+
Harkcom [82]																			SJC	
Van den Ende [30]						ns	ns							ns	ns				SJC	+
Baillet [31]	<i>NHP</i>	+	ns	ns	+	ns	ns	ns	ns	ns	ns	ns	ns						Ritchie	ns§
Neuberger [83]												***							S+TJC	+
Nordemar [84]																				+
Noreau [38]	<i>AIMS phys</i>	?										?							TJC	?
Lyngberg [57]																			TJC	ns

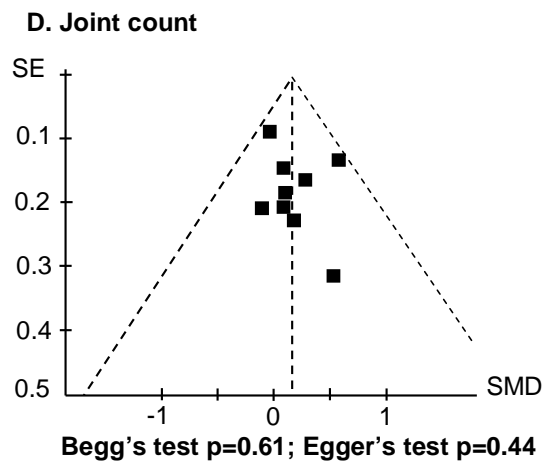
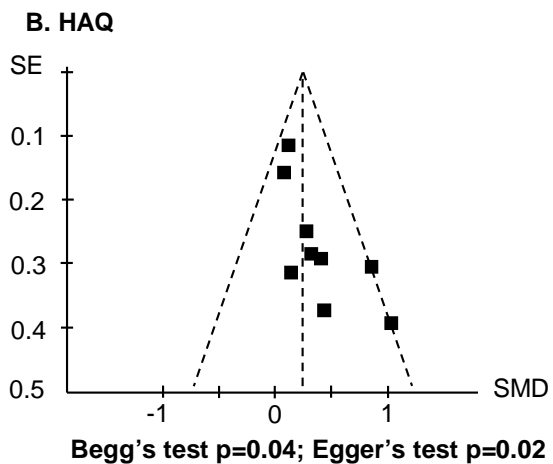
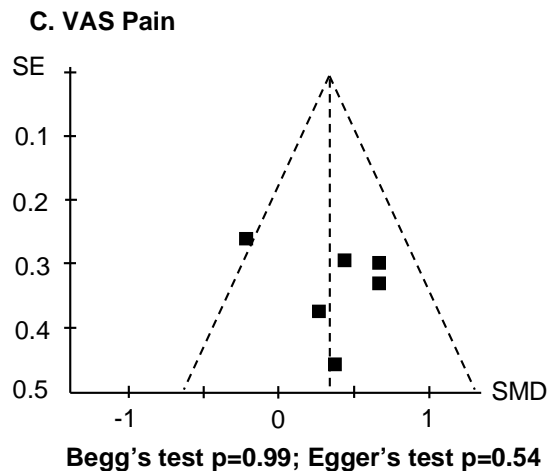
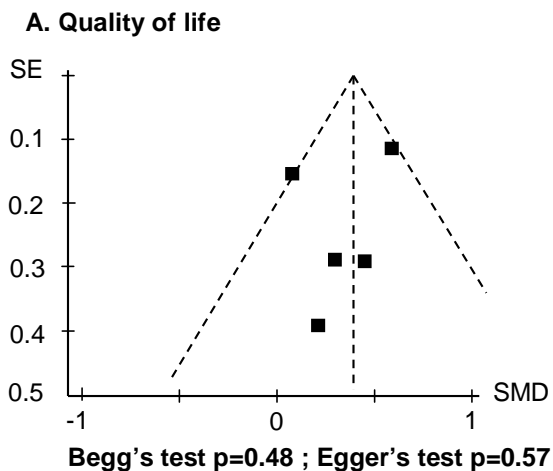
+ = Statistical difference in favor of exercise group; - = Statistical difference in favor of control group; ? = No statistical assessment of between-group difference; ns= no statistical difference between the two groups; \* = the difference between groups was significant for both feet only and feet/hand Larsen scores, but not significant for large joint Larsen score; \*\* = the difference between groups was significant at 3 weeks but not at 6 weeks; \*\*\* = the difference between groups was significant for pain intensity assessed by McGill scale; § = the difference between groups was significant for swollen joint count but not for the Ritchie index. HAQ = Health Assessment Questionnaire; DAS 28 = disease activity score; VAS = Pain Visual Analogue Scale; NHP = Nottingham Health Profile; RAQol = Rheumatoid Arthritis Quality of Life; SF36-Phys = physical component of the 36-item short-form health survey; AIMS = Arthritis Impact Measurement Scales Health Status Questionnaire; MACTAR = McMaster Toronto Arthritis; SJC= swollen joint count; TJC= tender joint count; S+TJC= swollen and tender joint count; mo = months

**SUPPLEMENTARY FIGURE 1. EFFICACY OF CARDIORESPIRATORY AEROBIC EXERCISES ON DISEASE ACTIVITY SCORE (A) AND RADIOLOGICAL DAMAGE (B).**



SMD = standardized mean difference (difference between both groups of mean outcome variation from baseline/SD at baseline); 95% CI = 95% confidence interval; IV = method of the inverse of the variance; DAS = Disease activity score; Larsen = Larsen's radiologic score.

**SUPPLEMENTARY FIGURE 2. PUBLICATION BIAS ASSESSMENT.**



Funnel plots for quality of life (A), function (B), visual analogue scale (VAS) pain (C), and joint count (D) meta-analysis. SMD = standardized mean difference; SE = standard error.

### **ANNEXE 3**

**Résultats supplémentaires publiés en ligne pour l'article 2 :**

**Baillet A, Vaillant M, Guinot M, Juvin R, Gaudin P.**

**Efficacy of resistance exercises in Rheumatoid Arthritis : Meta-analysis of  
randomized controlled trials.**

**Rheumatology (Oxford) 2011; en révision**

**TABLE 3 SUPPLEMENTARY MATERIAL. DEMOGRAPHIC CHARACTERISTICS.**

	Resistance exercises							Control group							
	Age, yr		RA onset, yr		n	Women		Completers	Age, yr		RA onset, yr		n	Women	
	mean	SD	mean	SD		%	%		mean	SD	mean	SD		%	%
Bearne L, 2002	nr	nr	nr	nr	47	nr	70.2	nr	nr	nr	nr	46	nr	71.7	
Boström A, 1998	56	24-74*	10.5	0.3-27*	24	100	83.3	59	42-74*	7	3-43*	21	100	81	
Buljina A, 2001	47.9	11.2	5.0	4.8	50	76	100	48.5	10.7	5.2	4.9	50	74	100	
Flint-Wagner HG, 2009	52.2	12.6	15.4	10.8	16	nr	nr	49	12.6	11.2	8.9	8	nr	nr	
Hakkinen A, 2001	49	10	0.8	0.8	35	51.4	88.6	49	11	0.7	1	35	57.1	88.6	
Hakkinen A, 1997	41.4	2.1	0,9	0,8	21	47.6	91.3	45.6	2.5	1,5	2	18	50.0	90.0	
Komatireddy GR, 1997	57.7	9.8	16.3	10.2	25	80	80	60.5	11	12.3	10.9	24	70.8	70.8	
Lemmey A, 2009	55.6	8.3	6.1	6.3	13	84.6	nr	60.6	11.2	10.1	8.4	15	80	nr	
Mc Meeken J, 1999	51.4	-11.1	nr	nr	17	88.2	100	49.7	-15.3	nr	nr	18	0	nr	
Van den Ende CH, 2000	62	13	8	8	34	58.8	82.4	58	14	7	8	30	66.7	66.7	

RA=Rheumatoid arthritis; SD=Standard deviation

**TABLE 4 SUPPLEMENTARY DATA. ADVERSE EVENTS (AE)**

	Resistance exercises	Control
Bearne L, 2002	4 flares, 9 unrelated to RA AEs	2 flares, 6 unrelated to RA AEs
Boström A, 1998	8 steroid injections	6 steroid injections
Buljina A, 2001	nr	nr
Flint-Wagner HG, 2009	nr	nr
Hakkinen A, 2001	1 unrelated to RA AE	none
Hakkinen A, 1997	6 unrelated to RA AEs, 1 back ache	5 unrelated to RA AEs, 2 back aches
Komatireddy GR, 1997	5 unrelated to RA AEs, 1 coronary artery disease	2 unrelated to RA AEs, 1 coronary artery disease
Lemmey A, 2009	nr	nr
Mc Meeken J, 1999	1 increased pain	1 diuretic prescription, 1 steroid injection
Van den Ende CH, 2000	5 unrelated to RA AEs, 1 psychological problem	5 unrelated to RA AEs, 1 psychological problem, 4 RA comorbidities

nr = not reported

**TABLE 5 ADDITIONAL MATERIAL. POOLED RESULTS FOR INVESTIGATED OUTCOMES.**

Outcome measures	Included studies (patients)	WMD/ RR, [95%CI]	p value	Heterogeneity I <sup>2</sup> , [95%CI]
Disability	9 (613)	WMD=-0.22, [-0.35, -0.10]	p<0.001	I <sup>2</sup> =36%, [0%, 69%]
Walk test	5 (275)	WMD=-1.90s, [-2.95s, -0.85s]	p<0.001	I <sup>2</sup> =35%, [0%, 75%]
Joint count	6 (390)	WMD=-5.36%, [-9.00%, -1.72%]	p=0.004	I <sup>2</sup> =73%, [12%, 86%]
Pain	5 (284)	WMD=-4.1mm, [-11.0, 2.7]	p=0.24	I <sup>2</sup> =54%, [0%, 82%]
ESR	3 (258)	WMD= -5.17mm, [-8.77, -1.58]	p=0.005	I <sup>2</sup> =0%, [0%, 73%]
Isokinetic strength	3 (148)	WMD=23.7%, [11.0%, 36.4%]	p<0.001	I <sup>2</sup> =0%, [0%, 73%]
Isometric strength	5 (300)	WMD=35.8%, [24.4%, 47.1%]	p<0.001	I <sup>2</sup> =68%, [0%, 86%]
Grip strength	4 (243)	WMD=26.4%, [12.3%, 40.5%]	p<0.001	I <sup>2</sup> =0%, [0%, 68%]
Adverse events	7 (378)	RR=1.08, [0.72, 1.63]	p=0.72	I <sup>2</sup> =0%, [0%, 59%]
Withdrawals	7 (371)	RR=0.95, [0.61, 1.48]	p=0.51	I <sup>2</sup> =0%, [0%, 50%]

Data) were pooled using inverse variance weighting and random effect methods. WMD=weighted mean difference; SE=standard error, RR=relative risk; 95%CI=95% confidence interval; ESR=Erythrocyte sedimentation rate



FIGURE 5 ADDITIONAL MATERIAL. LITERATURE SEARCH FLOW CHART.

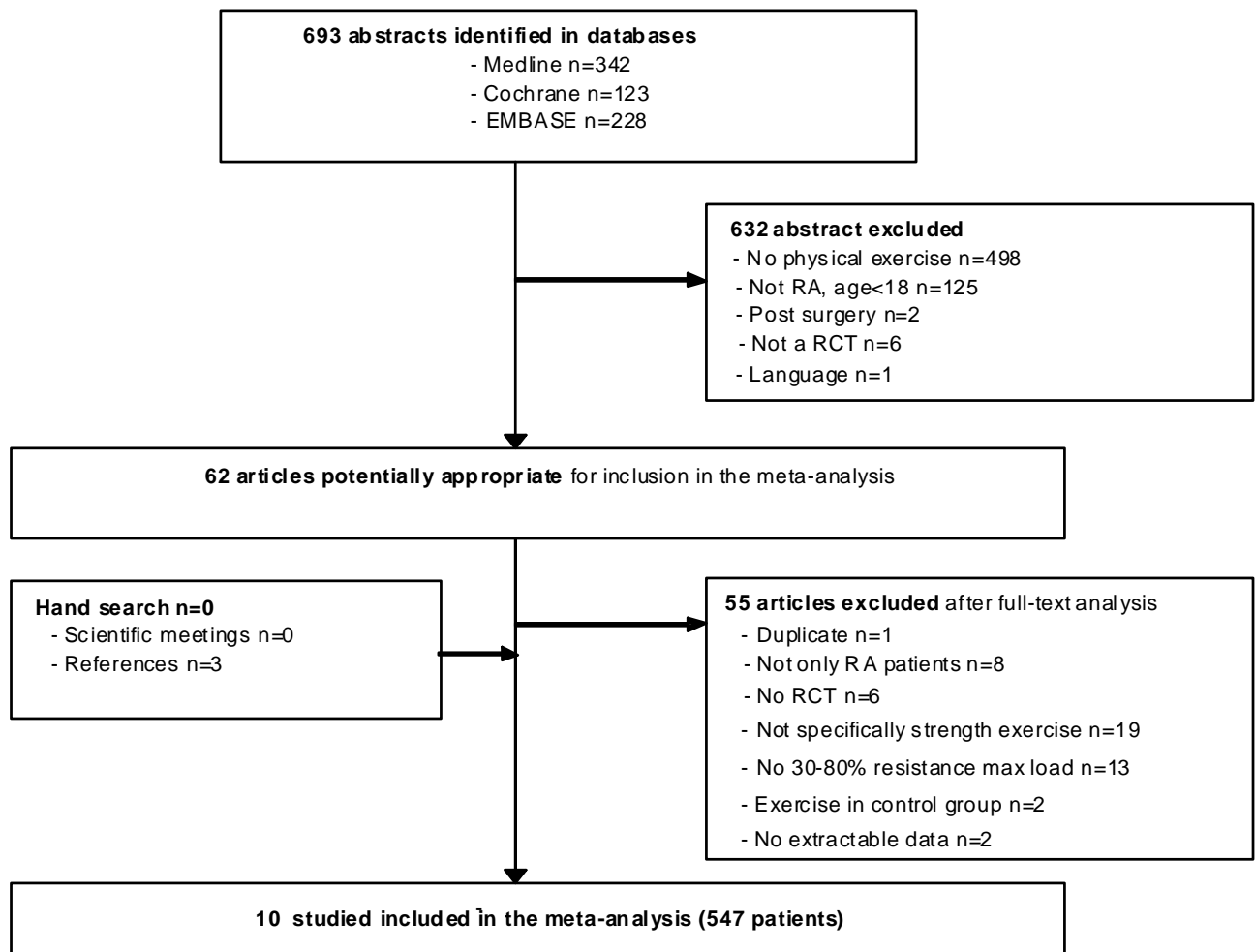
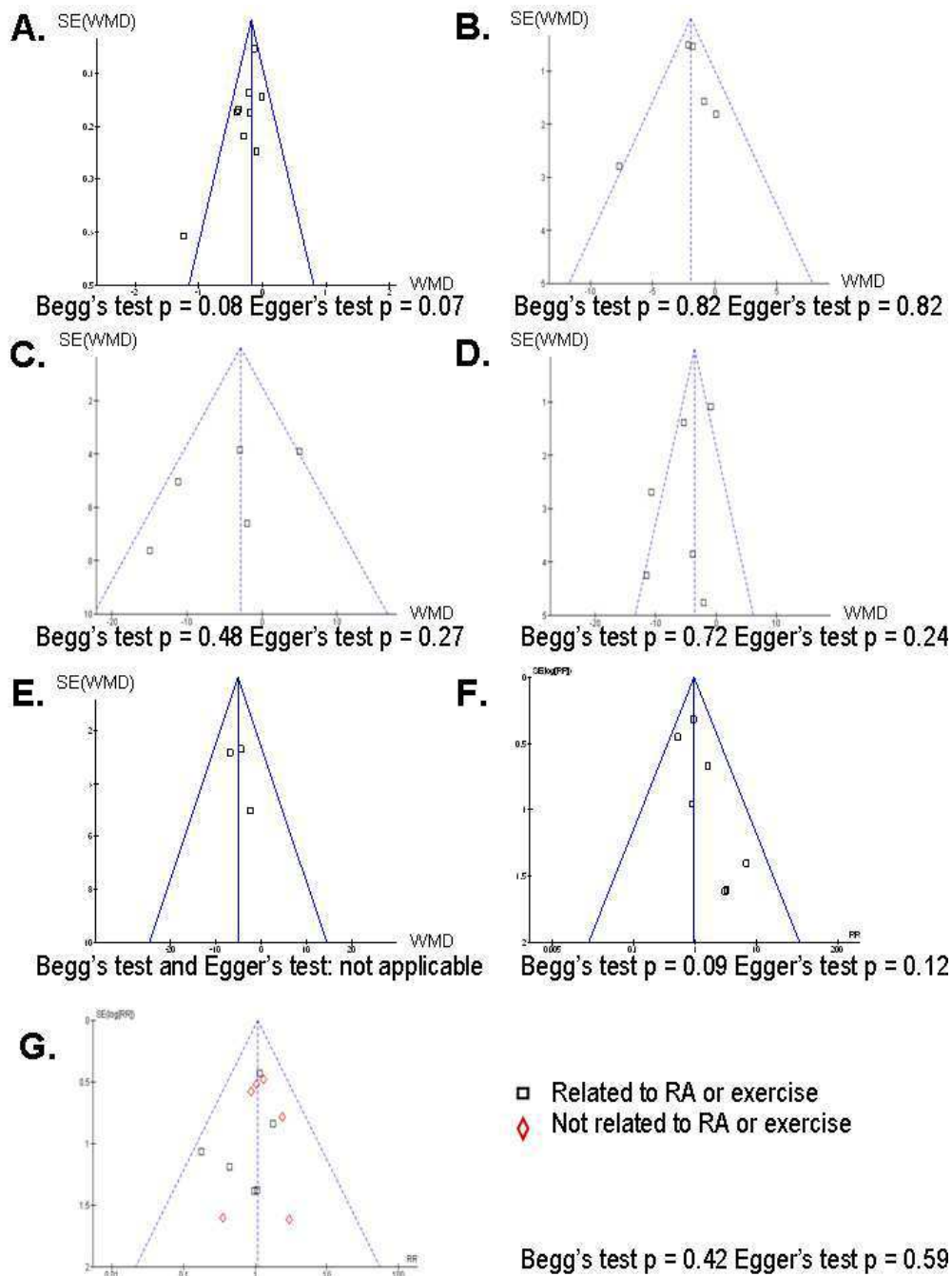
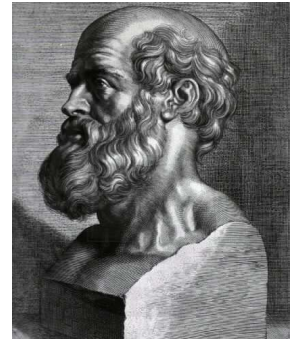


FIGURE 6 ADDITIONAL MATERIAL. PUBLICATION BIAS ASSESSMENT.



Funnel plots for resistance exercises vs. control concerning HAQ change (A), walking test (B), pain (C), joint count (D), Erythrocyte Sedimentation Rate at one hour (E), withdrawals (F), adverse events (G). WMD=weighted mean difference; SE=standard error, RR=relative risk.

## Serment d'Hippocrate



En présence des Maîtres de cette Faculté, de mes chers condisciples et selon la tradition d'Hippocrate, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent, et n'exigerai jamais un salaire au-dessus de mon travail.

Admis dans l'intérieur des maisons mes yeux n'y verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime.

Respectueux et reconnaissant envers mes Maîtres je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.