Exercise in older adults with rheumatoid arthritis

A person-centred approach

Elvira Lange

Department of Health and Rehabilitation
Institute of Neuroscience and Physiology
Sahlgrenska Academy, University of Gothenburg

UNIVERSITY OF GOTHENBURG

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elvira.m.lange@vgregion.se

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“It is the essence of certainty to be established only with reservations.”
Maurice Merleau-Ponty

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ABSTRACT

Physical activity and exercise are well known to enhance health and are recommended as part of the management of rheumatoid arthritis (RA). However, the level of physical activity among older adults with RA is found to be low and little research focuses on physical activity and exercise in older adults with RA.

The overall aim of this thesis was to study different aspects of exercise with person-centred guidance in older adults with RA.

Methods: A randomised controlled trial was performed to study the effects of exercise on disability, and health and fitness-related outcomes. Seventy-four older adults (>65 years) with RA were randomised to moderate- to high intensity exercise with person-centred guidance or light home-exercise for 20 weeks. After the randomised study a qualitative interview study was performed to explore how older adults with RA experience exercise, and aspects that affect the transition to independent exercise. Finally, a long-time follow-up study was performed to evaluate physical activity and physical fitness after four years.

Results: The result of the thesis show that exercise with person-centred guidance did not affect disability as assessed with the Health Assessment Questionnaire - Disability Index, but positive effects were found on physical fitness, fatigue, and symptoms of depression when compared to controls. The exercise was experienced as manageable and several aspects affecting the transition to independent exercise were described, including development of a personal way to exercise. After four years, there was no significant difference between groups, when change in physical activity level was compared.

In conclusion moderate- to high intensity exercise is beneficial for older adults with RA and is experienced as manageable and prepares the transition to independent exercise. This thesis supports the recommendation of physical activity as part of routine management of RA in adults above 65 years of age. However, maintaining exercise over several years is challenging.

Keywords: Exercise, Rheumatoid arthritis, person-centred, physiotherapy, aging

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SAMMANFATTNING PÅ SVENSKA

Reumatoid artrit (RA) är en ledsjukdom med smärta, trötthet och aktivitetsbegränsningar som vanliga symtom. Senare års forskning har visat att personer med RA har god effekt av fysisk aktivitet och träning och det är rekommenderat som del av handhavandet av sjukdomen. Dock är forskningen om träning för äldre personer med RA begränsad och äldre personer med RA är mindre fysiskt aktiva än friska äldre. Syftet med denna avhandling var att undersöka effekten av medel- till högintensiv träning för äldre personer med RA. För att underlätta genomförandet av träning vid smärta och aktivitetsbegränsningar användes ett personcentrerat förhållningssätt där fysioterapeuten tillsammans med deltagaren utformade och progredierande träningen.

Avhandlingen består av fyra delarbeten med det övergripande syftet att studera olika aspekter av träning med personcentrerad ledning för äldre personer med RA. Delarbete I och II baserades på en randomiserad, kontrollerad studie med 74 deltagare, där äldre personer (>65 år) fick träna styrka och kondition under ledning av fysioterapeut i 20 veckor medan en kontrollgrupp enbart utförde enklare hemträning. Det tredje delarbetet utforskade, genom djupintervjuer, upplevelserna av deltagandet i träningen och övergången till självständig träning sju månader efter interventionen. I delarbete IV följdes deltagarna upp efter fyra år beträffande fortsatt fysisk aktivitet och fysisk prestationsförmåga.

Resultatet visade att deltagarnas aktivitetsbegränsningar inte var signifikant påverkade av träningen när grupperna jämfördes. Dock sågs god effekt av träning på flera olika mått på fysisk prestationsförmåga och på trötthet och nedstämdhetssymtom. Träningen upplevdes som genomförbar och rustade deltagarna för övergången till fortsatt träning bland annat genom att de utvecklade kunskap och tankar samt gjorde träningen till sin egen. Efter fyra år var träningsgruppen signifikant mer fysiskt aktiv än vid inledningen av studien men det var ingen signifikant skillnad mellan grupperna.

Sammanfattningsvis visar avhandlingen att medel- till högintensiv träning är genomförbart och fördelaktigt för äldre personer med RA och rekommendationen att inkludera fysisk aktivitet och träning i handhavandet av RA är lämplig även för personer över 65 år. Att vidmakthålla träning i flera år är dock utmanande.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Lange E, Kucharski D, Svedlund S, Svensson K, Bertholds G, Gjertsson I, Mannerkorpi K. Effects of Aerobic and Resistance Exercise in Older Adults With Rheumatoid Arthritis: A Randomized Controlled Trial. Arthritis Care and Research 2019; 71: 61-70.

II. Kucharski D, Lange E, Ross A.B, Svedlund S, Feldthusen C, Önnheim K, Mannerkorpi K, Gjertsson I. Moderate-to-high intensity exercise with person-centered guidance influences fatigue in older adults with rheumatoid arthritis. Rheumatology International 2019; 39: 1585-1594.

III. Lange E, Palstam A, Gjertsson I, Mannerkorpi K. Aspects of exercise with person-centred guidance influencing the transition to independent exercise: a qualitative interview study among older adults with rheumatoid arthritis. European Review of Aging and Physical Activity 2019; 16:4.

IV. Lange E, Gjertsson I, Mannerkorpi K. Long-time follow up of older adults with Rheumatoid Arthritis after four years. *Manuscript.*

CONTENT

ABBREVIATIONS

1RM	One Repetition Maximum
ACR	American College of Rheumatology
BMI	Body Mass Index
CPET	Cardio Pulmonary Exercise Testing
DAS 28	Disease Activity Score
ESAI	Exercise Stage assessment Instrument
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
HADS	Hospital Anxiety and Depression Scale
HAQ-DI	Health Assessment Questionnaire Disability Index
ICF	International classification of function, disability and health
LTPAI	Leisure Time Physical Activity Instrument
MFI-20	Multi-dimension Fatigue Inventory
PGIC	Patient Global Impression of Change
RA	Rheumatoid Arthritis
STS	1-minute Sit to Stand test
TUG	Timed Up and Go
VAS	Visual Analogue Scale
WHO	World Health Organisation

DEFINITIONS IN SHORT

Disability	Umbrella term for impairments, activity limitations and participation restrictions. It denotes the negative aspects of the interaction between an individual (with a health condition) and that individual's environmental and personal factors. (WHO, 2013)
Exercise	Physical activity that is planned, structured, repetitive, and purposive to improve or maintain components of physical fitness. (Caspersen, 1985)
Independent exercise	Intentional physical activity performed outside of a health care setting, without guidance or coaching from health professionals. (Barkley, 2013)
Muscle power	Equivalent to energy output per unit time or the rate of doing work (Sapega, 1983)
Older adults	I this thesis defined as adults 65 years or older.
Person-centred	A patient is seen as a person in a personal context, with individual resources and limitations. Person-centred care is based on the establishment of a partnership with shared decision making and documentation. (Ekman et al., 2011).
Physical activity	Any bodily movement produced by skeletal muscles that results in energy expenditure. (Caspersen, 1985)
Physical fitness	A set of attributes that people have or achieve. The components are health-related or athletic abilities (Caspersen, 1985).
Self-efficacy	Perceived self-efficacy is concerned with people's beliefs in their capabilities to exercise control over their own functioning and over events that affect their lives. (Bandura, 1994).

1 INTRODUCTION

During the last decades, physical activity and exercise has been advocated as an important part of the treatment of rheumatoid arthritis (RA) (1, 2). Physical activity is also acknowledged for its general health benefits and prevention of diseases, especially in older age (3) (4, 5). It is well-known, however, that most persons physical activity is insufficient as 27.5% of the global population does not reach sufficient physical activity, which is known to be one of the strongest risk factors for several non-communicable diseases (6). Older adults are even less physically active (6) and persons with Rheumatoid Arthritis (RA) are less physically active than their healthy counterparts, especially older adults with RA (7, 8).

Persons with RA have described several barriers to exercise, including worries about that exercise could have negative consequences (9) (10). The use of a person-centred approach could be a way to manage barriers and worry and previous studies have used person-centred principles in exercise interventions with good results for adopting a physical activity behaviour and gaining benefits such as increased strength and reduced symptoms of disease (11, 12).

Using quantitative as qualitative methods, the studies in this thesis investigate different aspects of exercise and physical activity for older adults with RA. We hypothesised that moderate- to high-intensity exercise with person-centred guidance would be possible and manageable for older adults with RA and that they would gain health benefits similar to the benefits younger adults with RA gain from moderate- to high-intensity exercise.

1.1 AGEING

Ageing is described as ‘the progressive accumulation of changes with time associated with or responsible for the ever-increasing susceptibility to disease and death which accompanies advancing age’ (13). Adults are commonly categorised as older in relation to retirement age – 60-65 years in the developed countries (65 years in Sweden) (14). Depending on context and life expectancies, older adults have been defined from 50-75 years of age (15, 16). With modern advances in healthcare together with improvements in vital conditions, the part of the global population reaching the age of 65 is steadily increasing; by 2050, 25% of the European population will be older than 65 (17).

In normal aging, a decline of physical fitness is expected with a decline in muscle strength: 12-14% per decade after the age of 50 (18) and a reduction of aerobic capacity by up to 1% per year (19). A significant reduction of physical fitness is found between 60-70 years of age even without a reduction of physical activity (20). The risk factors for depressive symptoms also increase with age and approximately 15% of community-dwelling older adults show clinically significant depressive symptoms (21).

Several physiological changes are found related to aging including, genomic instability, mitochondrial dysfunction, and an altered intercellular communication, primarily inflammation (22). The inflammation process specifically related to aging is known as "inflam-aging (22). Inflamaging could lead to hormone reductions that cause bone fragility and muscle weakness (22). With advancing age, the skeletal muscle decreases in volume and is replaced by fat and connective tissue. The muscle fibres decrease in size and the number of muscle fibres decrease, especially type 2 fibres (fast muscle fibres) (23). Together, the decrease of muscle strength and a decrease in muscle power, related to disability, are found among older adults (24, 25). Muscular power is known to decrease with age independent of muscle cross section (26). Because muscular power is a stronger determinant for physical performance in older adults than muscle strength, power training is beneficial for functional performance in older age (25, 27). Power is defined as energy output per unit of time (28) and describes the ability to perform a muscular activity with high speed. Sarcopenia is the the loss of lean body mass, leading to an altered body composition, and is associated with impaired performance related to muscle weakness (29).

1.2 RHEUMATOID ARTHRITIS

Rheumatoid arthritis is a chronic autoimmune and inflammatory joint disease that is widely spread all over the world. In recent years, medical advances have widely decreased the effects of RA, but RA is still a substantial burden for the individual (30).

The most commonly described symptoms of RA are pain, tenderness, swelling, and stiffness of the joints, and fatigue (31, 32). Moderate and severe pain is found in about 70% of persons with RA (33). Typically, RA has a symmetrical distribution of synovitis, and small joints in hands and feet are often affected. These symptoms commonly lead to reduction of physical fitness and disability affecting everyday life. Approximately two-thirds of persons with RA suffer from inflammation-related cachexia, which leads to reductions in muscle mass and physical strength (34, 35). This alteration in body composition is found in

15-32% of patients with RA (36) and is related to disability, decreased physical fitness, and reduced muscle strength and walking speed (35, 37, 38).

For persons with RA, fatigue has been acknowledged as a very prominent and life disturbing symptom. Fatigue affects more than 40% of persons with RA (39) and RA-related fatigue is described as "an overwhelming sustained sense of exhaustion and decreased capacity for physical and mental work" (40). Often, fatigue is accompanied with symptoms of depression and anxiety (41). Depressive symptoms have been found among more than 50% of patients with RA and these symptoms are more common in the presence of high levels of pain (33).

With insufficiently treated RA, the risk increases for extra-articular manifestations of the disease, serious co-morbidities, and early death. The extra-articular manifestations could be vasculitis, noduli, and amyloidosis and the leading cause of RA-related co-morbidity is cardiovascular disease. However, all these risks are reduced, but not negligible, using modern treatments (30).

The global incidence of the disease is 40/100 000 each year, with a higher incidence in Europe and North America (42, 43). The incidence increases by double with age and peeks between 70-79 years old (44). The prevalence of RA according to the 1987 classification criteria is 0.77% in Sweden and women are two to three times more likely to be affected than men (45).

1.2.1 CLASSIFICATION CRITERIA

There are presently two sets of classification criteria for RA. The classification criteria published by Arnett et al. in 1987 describes a patient with a manifest disease (46). As treatment options have improved, it has become apparent that there is a need to identify patients with RA as early as possible and a new set of classifications criteria was developed in 2010 (47). The 2010 criteria create a more heterogeneous patient group (Table 1).

Table 1. The two sets of RA classification criteria.

ACR 1987 criteria	ACR/EULAR 2010 criteria	score
1. Morning stiffness	**A. Joint involvement (swollen or tender)**	
2. Arthritis of 3 or more joint areas	1 large joint	0
3. Arthritis of hand joints	2-10 large joints	1
4. Symmetric arthritis	1-3 small joints (with/without large joints)	2
5. Rheumatoid nodules	4-10 small joints (with/without large joints)	3
6. Serum rheumatoid factor	>10 joints (at least 1 small joint)	5
7. Radiographic changes	**B. Serology**	
	Negative RF and negative ACPA	0
	Low-positive RF or low-positive ACPA	2
	High-positive RF or high-positive ACPA	3
	C. Acute-phase reactants	
	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
	D. Duration of symptoms	
	<6 weeks	0
	>6 weeks	1
Four or more out of 7 criteria indicate definite RA. Criteria 1-4 must have been present for a minimum of 6 weeks.	The 2010 criteria consists of evaluation of four domains resulting in a score between 0-10 where a number ≥6 indicates definite RA.	

ARC: American College of Rheumatology; EULAR: European League Against Rheumatism; RF: Rheumatoid factor; ACPA: anti-citrullinated protein antibodies; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate

1.2.2 RHEUMATOID ARTHRITIS AND AGING

Aging of the immune system increases the risk for autoimmunity and RA and is accelerated by RA (48). With respect to immunity, persons with RA appear to be approximately 20 years older than their same age healthy counterparts (48, 49). Both aging and RA are associated with several comorbidities such as cardiovascular disease, malignancies, and osteoporosis (50). The accelerated aging of the immunity system in persons with RA also increases the risk for these comorbidities (49). The risk for many of these comorbidities, such as coronary heart disease and malignity, is known to be reduced by physical activity (51) .

To be presented with a comorbidity when already having RA (52) as well as dealing with age-related decline of physical fitness (53) is described as worrying. Joint damage due to RA increases every year one ages (54). For older adults with RA as well as healthy adults, high age is known to be associated with a reduction of physical activity (7, 8).

1.2.3 PATHOGENESIS AND MANAGEMENT OF RA

The origin of RA is unknown, but several risk factors have been described. Genetic factors play an important role in the development of RA (42); persons with a close relative with RA have a three times increased risk of developing RA (55). Environmental factors also play a role in the development of RA. The most commonly described environmental factors are smoking, with possibly a doubled risk for developing RA (56), infectious agents, compromised gastrointestinal microbiome, and an imbalance in glucocorticoid production by the hypothalamic-pituitary-adrenal axis (42). In recent years, research on pathophysiology and better treatment of RA have led to lower disease activity and preferential remission as treatment target (55).

A treatment to target strategy has been suggested, putting the patient in the centre recommending shared decisions between patient and rheumatologist. The primary goal of this treatment strategy is 'to maximise long-term health-related quality of life through control of symptoms, prevention of structural damage, normalisation of function and participation in social and work-related activities' (57).

Pharmacological treatment: Current pharmacological treatments of RA aim to decrease the disease activity and reach remission, or at least low disease activity using Disease Modifying Anti-Rheumatic Drugs (57). In recent years, the development has led to greatly expanded treatment options, including biologic therapies and janus kinase inhibitors (58). Metabolomic profiling, where residue from cell metabolism is analysed, has been suggested as a method to predict treatment response (59, 60). The research in this area is developing, possibly adding to the knowledge about the disease, for example, by adding bio markers (61).

Non-pharmacological treatment: Tailored patient education delivered throughout the course of the disease is acknowledged as an important part of the management of the disease. The education should be delivered by different professionals and experienced patients (62). In treatment of RA, the multidisciplinary team has been suggested to be important for both out- and inpatient settings (63, 64). However, the evidence for the efficiency of

multidisciplinary teams is limited (65). The team usually consist of rheumatologists, nurses, physiotherapists, occupational therapists, social workers and possibly also psychologists and dietarians (65). For example, non-pharmacological treatments delivered by the multidisciplinary teams are interventions to enhance self-management, hand-exercises, orthoses, foot-care, dietary interventions, physical activity promotion, and exercise (57, 66).

Physiotherapy: Physical activity and exercise are the primary recommended physiotherapeutic treatments in management of RA. In addition, physiotherapists should be part of the patient education strategy, focusing on educating patients about joint protection and coping with pain and disability. Electrical stimulation or thermotherapy is partly recommended as physiotherapeutic interventions and passive mobilisation could be used to preserve range of motion (67).

1.3 PHYSIOTHERAPY

Physiotherapy is a clinical practice and a science with movement as a central concept, both as the means and the goal. Movement contains several aspects affected by physical, social, and environmental factors. Physiotherapy is based in biopsychosocial perspective with both a bio-mechanical perspective and an existential perspective contiguous and also applied (68).

The primary goal of physiotherapy is to promote health and to maintain and regain optimal movement, function, and participation throughout life (68, 69). Movement and function could be threatened by ageing and disease, together with, for example, injuries, pain, and environmental factors. From a health perspective, persons are viewed as physical, psychological, social, and existential beings, so physiotherapists must have this holistic knowledge to improve movement and the overall health of their patients (68, 69). Closely related to movement is the concept of activity, which contains an action perspective on movement (68).

To classify health and health-related states in a broader perspective than solely describing the disease, the World Confederation of Physical Therapy has adopted the World Health Organisation (WHO) International Classification of Function, Disability, and Health (ICF) (70). This classification is suitable for physiotherapy as it adopts a biopsychosocial perspective, placing the person in a context (71). The classification contains the four domains of body functions, body structures, activities and participation, and environmental factors.

This thesis uses the ICF framework and uses the term physical fitness as an umbrella term for outcomes that are found in several domains of the ICF and are all closely related to movement. The term physical fitness include health-related fitness specified as cardio-respiratory endurance, muscular endurance, muscular strength, body composition and flexibility, and skill-related fitness such as agility, balance, coordination, speed, power, and reaction time (72).

With movement being the primary focus of physiotherapy, both physical activity and exercise are important parts of physiotherapy (73). The World Confederation of Physical Therapy emphasises that physical activity and exercise are important for health and wellbeing (69) and state that physiotherapists are experts on exercise throughout life (74).

1.3.1 PHYSICAL ACTIVITY AND EXERCISE

Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure (72). Exercise consists of physical activity that is structured, planned, repetitive, and with the purpose to improve or maintain one or more components of physical fitness (72). Exercise that is performed outside of a health care setting, without guidance or coaching from health professionals is defined as independent in this thesis (75).

The evidence for health benefits from physical activity is strong and physical activity is known to prevent several non-communicable diseases and reduce mortality. The WHO recommends a total of at least 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity aerobic physical activity each week together with muscle strengthening physical activities twice a week (3). For older adults, these recommendations are supplemented with balance training (3).

Aerobic physical activity. Aerobic physical activity uses large muscle groups in a way that can be continuous and rely on aerobic metabolism. Examples of these activities are walking, cycling, and jogging. Aerobic capacity is best assessed through maximal oxygen consumption (VO_2 max) (76). Aerobic physical activity has three components: Intensity – light, moderate, or vigorous; Frequency – how often the activity is performed; and Duration – length of activity (77).

Muscle strengthening physical activity. To strengthen muscles, physical activity involving moderate- to high load is necessary. Both resistance exercise and activities of daily living, such as carrying groceries and climbing stairs, could be included in muscle strengthening physical activity (78). Muscle strengthening physical activity has three components: intensity (weight or

force used); frequency (how often the activity is performed); and sets and repetitions (how many times an activity is repeated) (77).

Muscle power training. To increase muscle power, the concentric phase of an exercise should be performed at high speed (25, 79) with a load of approximately 40-60% of one repetition maximum (1RM) for optimal load (80, 81) to reduce the risk of injuries (79). For frail older adults, muscle power training is also suitable and it is important to introduce power training with a low load (approximately 20% of 1RM) and to gradually increase the load (82).

1.3.2 PHYSICAL ACTIVITY IN RHEUMATOID ARTHRITIS

During the 21st century, evidence for the benefits from physical activity among persons with RA has grown. In 2018, the European League Against Rheumatism (EULAR) developed recommendations on physical activity for persons with inflammatory arthritis that are feasible and safe (2, 83).

For working age adults with RA, aerobic and muscle strengthening physical activities increase aerobic capacity and physical function and decrease pain and disease activity (34, 84-86) as physical activity does not worsen the disease or increase oxidative stress (34, 87-89). Individual adjustments are necessary especially where severe joint damage is present (85). Physical activity in accordance to health enhancing recommendations for healthy adults also produces expected effects for persons with RA (88) and the effect seems to increase with increased intensity (90). In addition, despite strong evidence for benefits of physical activity, persons with RA are found to be less physically active than aged-matched healthy counterparts. This difference is most prominent among those above 55 years of age (7, 8). However, little research focuses on physical activity and exercise in older adults with RA.

Although symptoms of RA could entail difficulties performing physical activity (9), exercise levels below the general health recommendations still could be beneficial (3, 83). Physiotherapists strive to diminish the gap between preferred movement capability and actual movement capability (73). Therefore, physiotherapy can be important to facilitate physical activity and exercise in the presence of disease.

The symptoms of RA could entail difficulties with performing physical activity (9) why it is important to note that exercises levels below the general health recommendations still could be beneficial (3, 83). Physiotherapists strive to diminish the gap between preferred movement capability and actual movement

capability (73). That is why physiotherapy play an important role to facilitate physical activity and exercise in the presence of disease.

1.3.3 ADOPTION TO AND MAINTAIENCE OF PHYSICAL ACTIVITY

As there is low physical activity worldwide despite the known health benefits of physical activity, it is even more challenging for persons with RA to adopt and to maintain physical activity (91). For older persons, encouragement from friends, family, and clinicians might help them adopt and maintain physical activity. Strategies to overcome barriers for exercise might be necessary such as low costs, group activities, and supported enjoyment (92).

Physical activity depends not only on anatomic and physical components of the body but also on the motivation to move, which is related to thoughts, feelings, needs, and desires as human beings (73). The ability to be physically active is affected by contextual environmental factors and personal factors such as personality, attitude, emotions, and cognitive abilities (73).

To maintain physical fitness, physical activity must be maintained (3). However, maintaining physical activity is known to be difficult; among active exercisers as much as a third fails to maintain regular exercise for six months (93). Persons with RA are not only less active than heathy counterparts but also are less likely to maintain physical activity (8). Despite knowledge about the gains of physical activity and intention to perform, often there is gap between intention/knowledge and physical activity behaviour (94). To bridge this gap, physiotherapists need to note that physical activity requires new behaviours, and treatment outcomes might be improved through psychological techniques that address behaviour change (95). As promotors and rehabilitators, physiotherapists might be able to influence physical activity behaviour (96). Several psychological theories describe how to change physical activity behaviour. Two of these are described below: the Transtheoretical Model and the Self-determination Theory.

The Transtheoretical model. When engaging in a new behaviour, persons progress through six stages. The first stage is precontemplation, where no intention to changing the behaviour is present. The second stage is contemplation, which activates an intention to change behaviour. The third stage is preparation. The fourth stage is the action stage and the fifth stage is the maintenance stage. The last stage, termination, is where the new behaviour is fully integrated and a return to previous behaviour is unthinkable. The process through the stages might not progress evenly; there might be stops at

certain stages or even relapses (97, 98). In physiotherapeutic practice, it is important to meet the person at her current stage and tailor treatment and intervention based on the stage (97).

The self-determination theory. The self-determination theory discloses autonomous self-regulation and the power to make one's own mind up about what to do. Motivation in relation to personal needs is described as both intrinsic (e.g., personal joy or fulfilment) and extrinsic (e.g., an external reward) (96, 99). This theory focuses on environmental and social support where the physiotherapist facilitates engagement in self-care. For example, the physiotherapist could provide information that facilitates individuals informed decisions (96). Central in the social cognitive theory is to observe and interact with others, learning from behaviour and events. Experiencing mastery is acknowledged as a core element for personal change. This theory has led to the development of the concept of self-efficacy.

Perceived self-efficacy refers to a person's beliefs about her capability to perform specific tasks (100). Self-efficacy, important for motivation, affects thinking and behaviours that influence whether one adopts and maintains exercise. Developing self-efficacy requires experiencing accomplishments and could be increased by seeing other persons capabilities and though persuasion (100). In arthritis, self-efficacy is associated with pain, disability, as well as adherence to treatment and strategies, including patient education; in addition, increasing self-efficacy has been successful for self-management of the disease (101). Higher levels of self-efficacy, both for physical activities and for other areas in life, are seen in persons with arthritis that are physically active compared to inactive persons; this increased self-efficacy is also accompanied with higher beliefs in the benefits of exercise (102). For older adults, self-efficacy is known to play an important role both in adopting an exercise behaviour and maintaining exercise over time, and a decrease in self-efficacy in ageing has been found associated with becoming inactive (103). Self-efficacy could decline with advanced age together with an expectancy of declining abilities, but the experience and knowledge gathered through life could compensate for those losses to some extent (100).

1.4 PERSON-CENTREDNESS

In a Swedish context, the need for a more person-centred care has been acknowledged , and the Swedish Association of Local Authorities and Regions spreads knowledge about and implements person-centred care throughout Sweden (104). A shift to a more person-centred care is also central in the ongoing public inquiry 'Coordinated development for good and close care (*Samordnad utveckling för god och nära vård*) (105). A person-centred approach is an ethical point of view where the person receiving care is the focus. By acknowledging the person's context, resources, and limitations, the perspective is broadened from a view of a patient seen only in relation to and possibly limited by a disease. The cornerstones of a person-centred approach are the narrative, the partnership, and the documentation. To understand the person, the personal narrative, not only a collection of words but also through action and body, is an important carrier of information. By focusing on a person-centred partnership, the relation between patient and caregiver becomes important, and from a philosophical perspective the meeting between humans could be viewed as existentially essential. The documentation gives a structure to the approach and it is important that the documentation is ongoing and shared between patient and caregiver so that information and decision-making truly becomes shared (106). A more person-centred approach in healthcare is considered to make healthcare more equal and efficient (105).

Persons with RA desire a person-centred approach in healthcare where a partnership with shared endeavours is the focus, and they want clinicians to use openly communicate and show empathy (107). To develop adequate healthcare for older adults with RA, possibly living with emerging comorbidities, a disease-centred perspective is not sufficient; a goal-oriented and person-centred approach is needed (50).

A person-centred approach is the basis for clinical reasoning in physiotherapy (68). Six components of person-centred physiotherapy have been acknowledged: self-management; individualisation; decision making; information sharing; goal setting; and ongoing care (108). Partnership is important to incorporate in all components; for example, goal setting requires a mutual understanding of what is meaningful for the patient (109). Person-centred physiotherapy has successfully been used in studies to promote physical activity (12) and initiating exercise (11).

2 AIM

This thesis studies how exercise with person-centred guidance affects older adults with RA.

Specific aims for the four studies are listed below.

Study I

To study the effect of moderate- to high intensity aerobic and resistance exercise with person-centred guidance on disability and physical fitness for older adults with RA, compared to controls.

Study II

To study the effect of moderate- to high intensity aerobic and resistance exercise over 20 weeks on fatigue and symptoms of anxiety and depression in older adults with RA, compared to controls.

Study III

To explore expereinced aspects of participation in moderate- to high intensity exercise with person-centred guidance that influences the transition to independent exercise for older adults with RA.

Study IV

To evaluate how level of physical activity and physical fitness were affected after four year by participation in moderate- to high intensity exercise with person-centred guidance, among older persons with RA, compared to controls.The aim was also to study which factors influence increase of physical activity after four years.

3 METHODS

This thesis consists of four studies. Based on the research questions, different methods have been used for recruitment, data collection, and analysis. Study design, recruitment, population, data collection, and methods of analysis are presented in Table 2.

Table 2. Schematic overview of the research design of the studies

	Study I	**Study II**	**Study III**	**Study IV**
Study design	Randomised controlled multi-center study	Secondary analysis of a randomised controlled study	Qualitative exploratory Interview study	Prospective, controlled, long-time follow up
Recruitment	Sample recruited from register		Recruited from Study I	
Study population	Older adults with RA			
Number of participants	n=74 Intervention group (n=36) Control group (n=38)		n=16 All recruited from Intervention group	n=47 Intervention group (n=24) Control group (n=23)
Data collection	Clinical examination Standardised interview on demographics Self-reported questionnaires Performance-based tests	Clinical examination Standardised interview on demographics Self-reported questionnaires Blood sampling	Semi-structured individual in-depth interviews	Clinical examination Standardised interview on demographics Self-reported questionnaires Performance-based tests
Analysis	Non-parametric statistics Parametric statistics		Qualitative content analysis	Non-parametric statistics Parametric statistics Regression analysis

3.1 PARTICIPANTS (STUDY POPULATION)

The characteristics of the participants are presented in Table 3. The groups were considered equal regarding baseline characteristics. In Study III, a small sample was recruited from the original cohort, and their characteristics were considered equal to the original cohort. In Study IV, all participants from the original cohort were invited and 63.5% of the original cohort participated (Figure 1). The included study population of study IV was not statistically different regarding characteristics at baseline from those not taking part.

Table 3. Characteristics of the study population in each of the studies

	Study I & II	**Study III**	**Study IV**
Sex (female)	77%	69%	77%
Age (years)	70 (2.49)	71 (3.05)	74 (2.4)
Disease duration, years	16 (10.8)	13 (10.5)	20 (10.5)
Body mass index	26.8 (4.6)	25.6 (4.1)	26.2 (4.6)
VAS Pain, current (mm)	21.9 (17.4)	16 (19.7)	29.5 (24.1)
HAQ-DI	0.56 (0.49)	0.49 (0.59)	0.55 (0.53)
LTPAI (h):			
Light	3.5 (3.64)	3.9 (4.78)	4.1 (3.10)
Moderate	2.2 (1.97)	2.4 (2.5)	3.6 (3.88)
Vigorous	0.6 (0.87)	0.3 (0.49)	1.2 (1.62)
ESR	13 (10.3)	17 (14.4)	18 (10.8)
CRP	5.4 (11.6)	10.5 (24.1)	3 (2.6)
DAS 28	2.37 (0.99)	2.35 (1.09)	2.91 (0.85)

Number given as mean and Standard Deviation. VAS: Visual Analogue Scale; HAQ-DI: Health assessment questionnaire Disability Index; LTPAI: Leisure Time Physical Activity Instrument; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; DAS 28: Disease Activity Scale 28.

3.1.1 RECRUITMENT

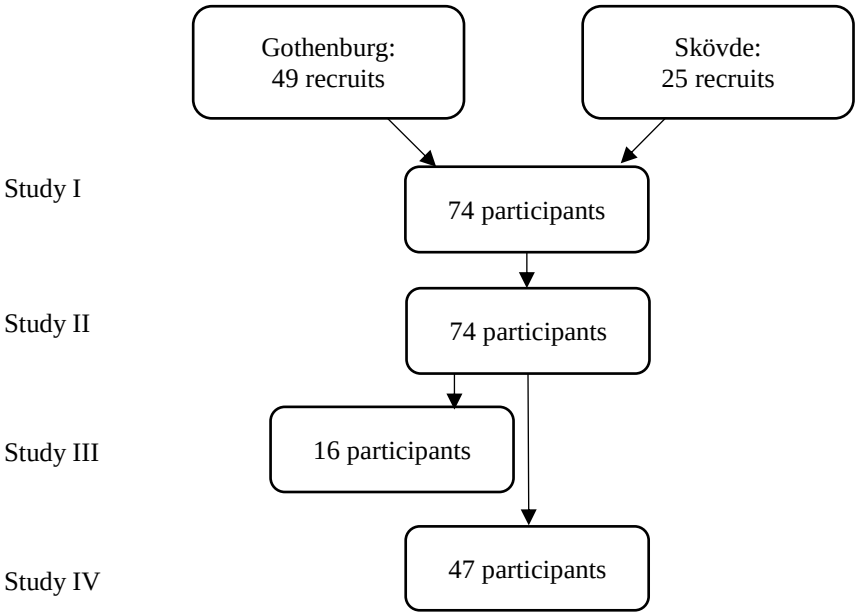

Figure 1. Study populations and number of participants included in each study.

The inclusion and exclusion criteria for Study I and Study II are listed below:

Inclusion criteria:

- RA according to the ACR 1987/EULAR 2017 criteria (46, 47)
- age ≥65 years; disease duration >2 years
- low to moderate disease activity score (DAS 28 <5.1)

Exclusion criteria:

- co-morbidities such as unstable ischemic heart disease or arrhythmia that might preclude moderate intensity exercise
- joint surgery within six months before inclusion
- on-going exercise of moderate- to high intensity ≥2 times/week
- inability to understand or speak Swedish
- inability to participate in physical testing that involved walking or bicycling

Study I and Study II

The Swedish Rheumatology Quality register (44) was used to identify 1028 older adults (≥65 years) with RA in the Gothenburg and Skövde area in the Region Västra Götaland. After screening of medical records for inclusion criteria, 488 persons were invited to participate via letter, which was followed by a phone call. Based on information gathered during the phone interview, 121 persons were invited to a screening visit with a medical exam. Finally, 74 persons were included in the studies and randomised (Figure 2).

Study III

From the exercise group of the intervention study, 16 participants were consecutively recruited after completing all assessments of the intervention study 12 months follow-up. Both male and female subjects were included in the study and participants were recruited from both the Gothenburg cohort with two study groups and the Skövde Cohort. No invited subject declined participation.

Study IV

Four years after inclusion of the intervention study, all participants who performed post-intervention assessments were invited to take part in a long-time follow-up study. The invitation was sent to 70 participants and followed by a phone call; 47 persons agreed to participate.

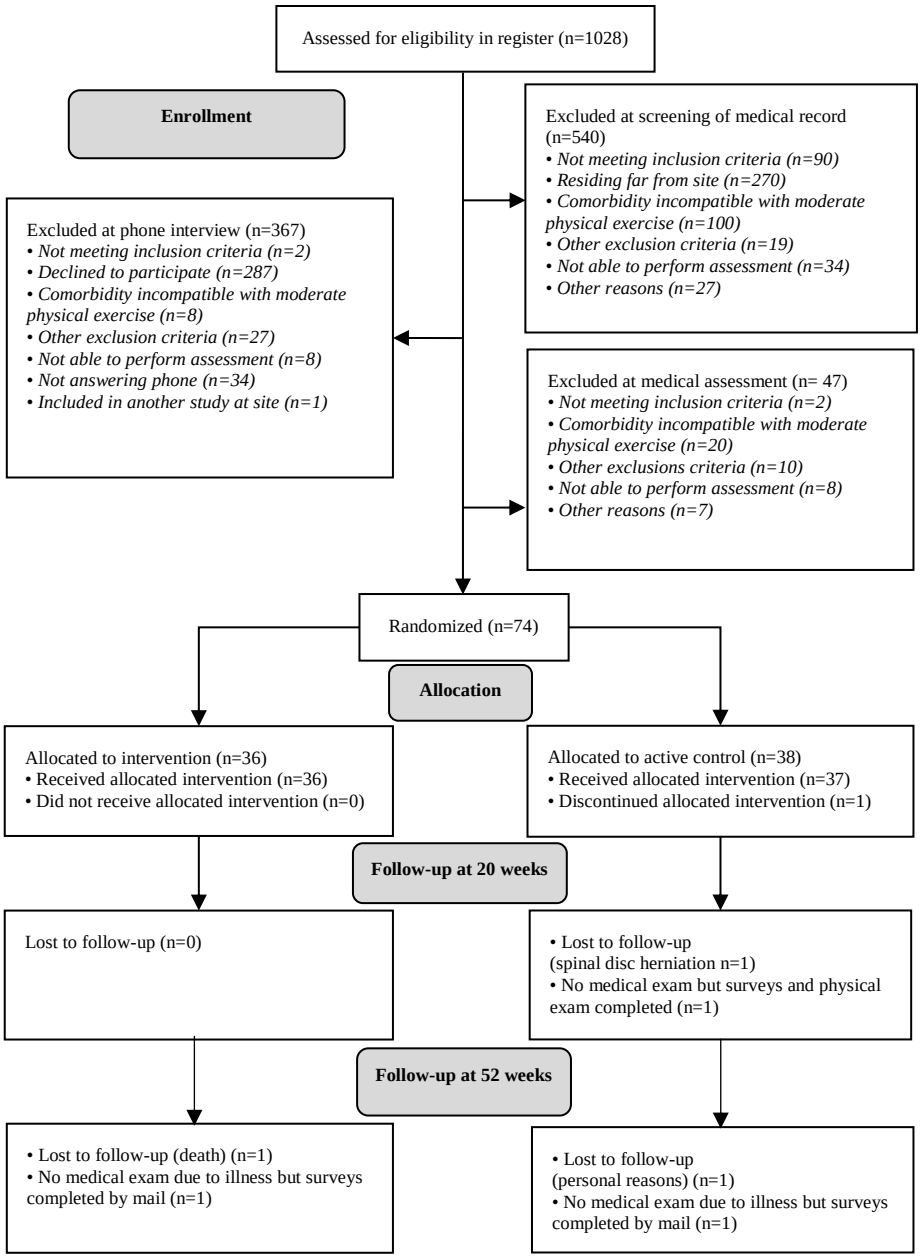

Figure 2. CONSORT diagram for Study I and II. Original figure from publication (110) used with permission according to Creative Commons Attribution Non-Commercial No Derivatives License CC BY-NC-N.

3.1.2 DATA COLLECTION

Assessment methods for the studies are listed in Table 4 and are described in more detail in the following section. For each study, the examinations were performed by an assessor who was blinded to the group allocations.

Demographic data

Background data were collected via a standardised interview and included sex, age, time (years) since diagnosis, education level, civil state, medication use, and tobacco use.

Clinical examination

Blood sampling was performed and concentrations of Erythrocyte sedimentation rate, C-reactive protein, and haemoglobin were measured by the accredited routine laboratories for clinical chemistry at Sahlgrenska University, Gothenburg, and at Unilabs, Skövde. Fasting blood plasma was collected to analyse metabolomics and plasma metabolomics were measured using mass spectrometry. A joint score was registered (111) as well as a score for self-reported global health on a visual analogue scale (VAS) to calculate the DAS 28 based on Erythrocyte sedimentation rate (112). Body weight (kg) and height (m) were measured and registered to calculate body mass index (BMI= kg/m^2).

Self-reported questionnaires

The Health Assessment Questionnaire – Disability Index (HAQ-DI) was used to assess general disability by measuring eight aspects of activity in the last week rated on a scale from 0 to 3 (113). A total mean score was calculated from the eight aspects with a lower value indicating less severe disability. The Swedish version shows good validity and reliability in patients with RA (114). The sensitivity is limited in the normal function range (115, 116).

The Leisure Time Physical Activity Instrument (LTPAI) was used to assess hours of weekly physical activity based on self-reported hours of low, moderate, and vigorous activity the last week. The results were presented as a sum of moderate to vigorous activities, a sum of all activities or separately for each category. The validity and reliability have been found sufficient in persons with fibromyalgia (117).

The Patient Global Impression of Change (PGIC) was used to assess the patient's perceived change in health. PGIC is a one-item scale that ranges from 1 (very much improved) to 7 (very much worse) (118). PGIC was measured at the post-intervention examination and at the 12-month follow-up.

A Visual Analogue Scale (VAS) was used to assess pain and fatigue (119). The participants were asked to rate current pain and current fatigue on a 100-mm line with the anchors 'no pain/fatigue' and 'worst possible pain/fatigue'. VAS is widely used in in rheumatology and has been tested with sufficient reliability and validity (120).

The Multi-dimension Fatigue Inventory (MFI-20) was used to assess five different dimensions of fatigue (121). It is a questionnaire with 20 items rated between 1 and 5. The subscales are general fatigue, physical fatigue, mental fatigue, reduced activity, and reduced motivation. The items of each subscale are added together to give a result between 4 and 20 where a higher value indicates less fatigue. The Swedish version is considered valid and reliable (122, 123) .

The Hospital Anxiety and Depression scale (HADS) was used to assess anxiety and symptoms of depression. HADS consists of 14 questions rated between 0 and 3 with the results divided into the subscales Anxiety and Depression (124). The subscales range between 0 and 21, and a cut-off of eight and above has been suggested to identify anxiety and depression disorders (125). The validity and reliability of HADS in RA is good, especially with the cut-off of eight (126).

The Modified Exercise Stage Assessment Instrument (ESAI) was used to assess maintained physical activity (127, 128). It is a questionnaire where physical activity is defined according to the WHO recommendations for health (129) and followed by two five-choice questions with the options based on the stages of change in the transtheoretical model (98). The first question concerns aerobic physical activity for $\geq$ 30 minutes for $\geq$ 5 days/week and the second question concerns resistance exercise twice a week.

Performance-based tests of physical fitness

Assessment of aerobic capacity through a Cardiopulmonary Exercise Test (CPET) was performed according to a modified protocol from the American Heart Association guidelines (130). The equipment was calibrated according to the manufacturer's specifications before each test. A symptom-limited bicycle ergometer test was performed with a continuous workload protocol such that the test lasted 8-10 minutes. Ventilatory expired gas analysis was

performed using a metabolic chamber (Jaeger OxyCon Pro; Intramedic AB, Sollentuna, Sweden). Standard 12-lead electrocardiogram was used and blood pressure levels were determined at rest and every other minute during the exercise regimen. The maximal oxygen consumption per kg body weight per minute (VO_2/kg/min) was analysed.

A bicycle endurance test was performed (131) as a complement to the CPET on an electronically-braked cycle ergometer (M*onark Ergometer* 839 E; Monark Exercise AB, Vansbro, Sweden). After a two-minute warm-up at 50 W, the participants cycled at a constant power of 70% or 75% of the maximum achieved power, which was based on the estimation from the CPET, and the total time was registered when the level of exertion was rated a 'Very hard' on the Borg rating of perceived exertion (132).

Functional mobility and dynamic balance were assessed with the Timed Up and Go (TUG) test where the participants were asked to perform the following series: rise from an armchair; walk a distance of 3 m as quickly as possible but still safely; walk back; and sit down (133). The entire task was timed. The test has shown good reliability in a Swedish population of patients with RA and is sensitive to change (134, 135).

Leg muscle function was assessed using the Sit to Stand (STS) test (136). The number of complete rises performed in 60 seconds was recorded. The test is valid and has been shown to correlate to muscle strength in the lower extremities in a Swedish middle-aged to aged population (137). The reliability of the STS test is also satisfactory (138).

Isometric elbow flexion force was assessed with an electronic dynamometer. Different models of the device were used at the two sites: the Isobex and the newer Isoforce Control® (Medical Device Solutions AG, Oberburg, Switzerland). All the subjects were assessed with the same device at every repeated assessment. The participants were seated in a standardized position without back support with legs stretched out. The forearm was supported by the trunk with the elbow at 90° flexion, and the maximum force in elbow flexion was measured. This instrument has been shown to be reliable for measuring shoulder force (139, 140) and has been used to measure elbow flexion force (141).

Table 4. Outcome measures used in Study I-IV

Outcome	Description	Unit	Range, best-worst	Number of items	Item range	Used in study
Self-reported questionnaires						
HAQ-DI	Disability-index		0-3	8	0-3	I
LTPAI	Weekly physical activity	Hours	-	4	-	I, IV
PGIC	Self-rated change in health		-	1	1-7	I
VAS fatigue	Current fatigue	mm	0-100	1	0-100	II
VAS pain	Current pain	mm	0-100	1	0-100	II
MFI-20	Five dimensions of fatigue		20-4	4×5	1-5	II
HADS	Anxiety and depressive symptoms		0-21	7+7	0-3	II
ESAI	Current and maintained physical activity		-	2	1-5	IV
Performance-based tests						
CPET	Maximum oxygen consumption	ml				I, II
Endurance test	Endurance on bicycle	min				I, IV
TUG	Mobility and dynamic balance	sec				I, IV
STS	Leg muscle function through rise from chair	Number				I, IV
Elbow flexion force	Dynamic elbow flexion force	Newton				I

HAQ-DI: Health Assessment Questionnaire-Disability index; LTPAI: Leisure tome physical activity Instrument; PGIC: Patient global Impression of Change; VAS: Visual analogue scale; MFI: Multi-dimension Fatigue Inventory; HADS: Hospital Anxiety and Depression scale; ESAI: Exercise Stage assessment Instrument; CPET: Cardio Pulmonary exercise test; TUG: Timed Up and Go; STS: Sit to Stand test

Qualitative interview

Data for Study III were collected through semi-structured in-depth interviews performed individually by a physiotherapist who had no previous relation to the participants. After pilot testing of an interview guide, the same interview guide was used. The guide included open questions about experiences of the exercise with person-centred guidance and the transition to independent exercise. The interviews lasted 45-60 minutes and were audio recorded. The interviews were transcribed verbatim and the transcripts became the unit of analysis.

3.1.3 PROCEDURCE

Study I

At the start of Study I, the participants attended a screening visit with a medical exam followed by baseline examinations and assessments. A clinical examination, blood sampling, self-reported questionnaires, and performance based tests, described above, were used. After inclusion, the participants were randomised to either moderate-to high intensity exercise with person-centred guidance or to an active control group. The randomisation was performed by an independent person not involved in the study and conducted separately for each site. Sealed, opaque envelopes were used with a computer-generated sequence of allocation. The participants were randomised in a block of six subjects and randomisation were stratified by gender (men/women) and site (Gothenburg/Skövde).

A physiotherapist introduced both groups to a light home-exercise program to be performed twice a week together with moderate aerobic physical activity for 150 minutes a week according to current health enhancing recommendations (3). In addition, the exercise group was also assigned a 20 week exercise intervention, developed based on a previous protocol (142). The intervention consisted of both aerobic and resistance exercise with a moderate-to high intensity performed three times each week. Two of three exercises sessions each week were supervised by a physiotherapist offering a person-centred introduction and guidance of the exercise. The sessions started with a light warm up for mobility and five minutes of light aerobic warm up. The aerobic exercise was performed in sets of three minutes, initially three sets and continuously increased to nine sets over nine weeks. The participants were encouraged to perform the exercises maintaining a heart rate of 70-89% of maximal heart rate, which was verified with heart rate monitors and ratings of the Borg rating of perceived exertion scale (132) between 14-16 (143). The

resistance exercise consisted of five exercises and were performed in two sets of 8-12 repetitions at approximately 80% of 1RM. After 12 weeks, one set of power training was added to each exercise. Assessments were performed directly after the end of the 20 week exercise intervention and follow-up was performed 12 months after baseline.

Study II

The procedures in Study II were the same as in Study I together with sampling and analysis of metabolomics in the Gothenburg part of the cohort at baseline and after 20 weeks.

Study III

The participants in the qualitative interview study were assigned to one individual interview session performed at the hospital where Study I and II were performed.

Study IV

In Study IV, the participants attended one visit at the research department for performance based tests, blood sampling, and self-reported questionnaires. All assessments were performed by the research nurses who had been involved in the previous studies.

3.1.4 ETHICS

Ethical approval for Studies I-III was obtained from the Regional Ethics Board in Gothenburg and for Study IV from the Swedish Ethical Review Authority. All studies complied with the Declaration of Helsinki (144).

Several ethical issues were considered when designing the studies. In Study I, the demands of the participants were high considering time both in the data collection with several appointments and in the interventions with three exercise sessions each week. However, the gains for the participants were considered higher both in getting a rigorous medical exam and getting a through introduction to exercise without any cost. For Study I, there were also ethical considerations concerning the control intervention. With the best interest of the participants in mind, the control intervention was designed according to current recommendations on health enhancing physical activity and clinical praxis.

For Study II, the already mentioned considerations were also valid. Besides this subgroup, analysis of metabolites was performed based on gender with significant results, but these results were not published based on the small group size (men, n=5) and large standard deviation (SD).

For Study III, the interview guide was reviewed for questions of a sensitive character. The questions were considered unlikely to be of a sensitive and of upsetting character and at the same time a plan was made for management of participants reacting with strong feelings to the interview. None of the participants did.

For Study IV, the risk of the research questions being experienced inconvenient was considered and all participants were offered a consultation with a physiotherapist, which nine persons accepted.

3.2 ANALYSIS

To answer the different research questions, different analytical methods were used. In the following section, the different statistical analysis and the qualitative content analysis are described.

3.2.1 STATISTICAL ANALYSIS

Statistical analysis were performed mainly with the Statistical Package Software for the Social Sciences ver. 24.0 (IBM Corp., Armonk, NY, USA). For Study II, analysis were made with Graph Pad Prism (GraphPad. San Diego. USA). The significance level was set to 0.05 and all significance tests were two-sided.

For Study I, comparisons of change were made between groups with non-parametric Mann-Whitney U test for the primary outcome HAQ-DI. For the continuous variables, the parametric Students t-test was used for between group comparisons. Within group comparisons were performed with Wilcoxon signed rank test or pared Samples t-test based on data level.

Analysis of Study II was made with Mann-Whitney U test for non-parametric variables and Student's t-test for non-parametric variables for between group comparisons and Wilcoxon signed rank test for with-in group comparisons. Correlations were performed with Spearmans's correlation. The analysis of metabolomic data was performed with General Linear Model to identify differences in metabolic response. The data were log-transformed and corrected for baseline.

The comparisons of Study IV were performed with Mann-Whitney U test and Wilcoxon signed rank test. A logistic regression model was built to search for association with increased physical activity after four years. The rating of LTPAI was dichotomised as equal and lower than baseline or higher than baseline.

Table 5. Overview of statistical test included in the studies

	Study			
Statistical test	**I**	**II**	**III**	**IV**
Descriptive statistics				
Mean (SD)	X	X	X	X
Median (min/max)	X	X	X	X
Number (n) and percent (%)	X	X	X	X
Comparisons between groups				
Student's t-test	X	X		
Mann-Whitney U-test	X	X		X
Chi-square test				X
Within-group comparison for change				
Paired Samples t-test	X			
Wilcoxon signed rank test	X	X		X
Estimate of magnitude of change				
Effect size	X			
Analyses of correlations				
Spearman's correlation		X		
Pearson's correlation		X		
Regression analysis				
Multivariate logistic regression analysis				X
General linear model		X		
Determination of sample size				
Power analysis	X			

SD: Standard deviation.

3.2.2 QUALITATIVE CONTENT ANALYSIS

The qualitative content analysis was performed according to Graneheim and Lundman (145). The transcripts of interviews were read through to gain a sense of the whole. Text elements that met the research questions were chosen as meaning units. The meaning units were not to be too broad as this would risk containing several meanings; however, the meaning units were not to be too narrow as this would risk losing meaningful content. The meaning units were then condensed: i.e., the text was shortened without losing its core content. Through the analysis process, the meaning units formed categories and sub-categories. The processes moved between the parts and the whole text to not lose the context of the meaning units.

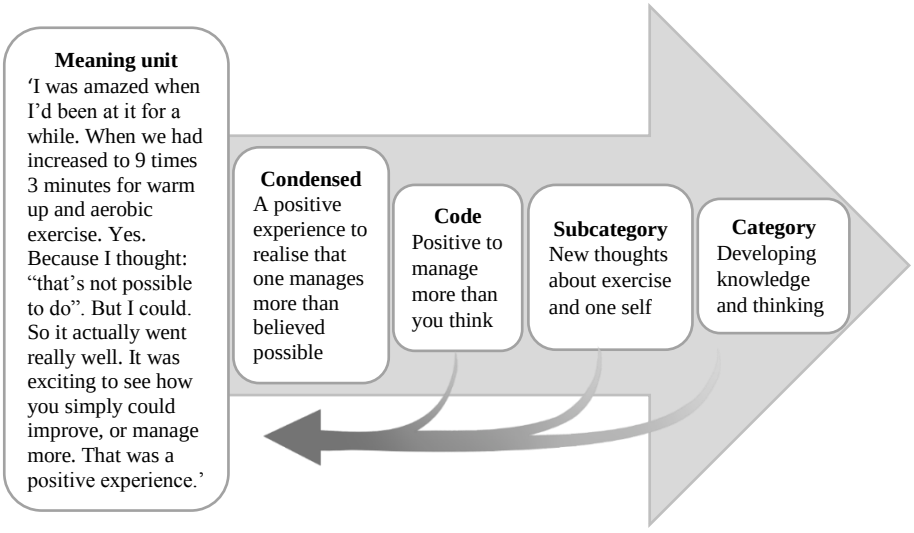

Figure 3. Schematic figure of the qualitative analysis process. Original figure from publication (146) used with permission according to the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

4 RESULTS

A summary of the results of Study I-IV is presented in the following section. Characteristics of all four studies are presented in Table 3. Since Study IV is not published, the results are presented briefly.

4.1 STUDY I

Exercise with person-centred guidance improves physical fitness

All participants in the exercise group completed the intervention and post-intervention assessments and all but one participant in the control group fulfilled the same. Adverse effects, i.e. increased pain that could be related to exercise, led to persistent exercise modifications for four participants in the exercise group and nineteen participants experienced temporary increase pain, managed without modifications or with temporary modifications.

The results of Study I show that the primary outcome HAQ-DI was not significantly changed when groups were compared. However, a significant improvement from baseline was found with-in the exercise group (p=0.022). Four of five performance-based tests were improved in the exercise group when compared to the control group (Table 6). Self-rated improvements of health on the PGIC were significantly higher in the exercise group than in the control group.

At the 12-month follow-up, 93% of the participants (n=69) completed all assessments. At this point, the exercise group rated a significantly increased moderate- to high intensity weekly physical activity level (mean: 2.2 hours) on LTPAI (p=0.005). Based on exercise diaries and phone calls, 18 participants of 35 in the exercise group were exercising with a similar intensity during the follow-up period as during the intervention and 12 were exercising but with a lower intensity. During the follow-up period, the control group performed home exercise 1.9 times /week on average.

When the results of the 12-month follow-up were compared to baseline, the only significant difference between groups were found in the endurance test with and mean increase of 4.7 minutes in the exercise group (p=0.022).

Table 6. Between group analysis of change of the outcomes of Study I

	Exercise group week 0	week 20	week 52	Control group week 0	week 20	week 52	Analysis of change, between groups	
Measures	Mean (SD) Median (range)	Mean (SD) Median (range)	Mean (SD) Median (range)	Mean (SD) Median (range)	Mean (SD) Median (range)	Mean (SD) Median (range)	20-0 p-value	52-0 p-value
HAQ-DI	0.52 (0.5)	0.45 (0.49)*	0.5 (0.51)	0.6 (0.48)	0.58 (0.48)	0.63 (0.54)	0.200	0.258
	0.38 (0;1.75)	0.31 (0;1.75)	0.38 (1;1.75)	0.44 (0;1.5)	0.38 (0;1.75)	0.5 (0;1.75)		
VO²/kg/min, ml	18.6 (3.8)	20.92 (3.7)**	-	17.8 (3.81)	17.46 (3.76)	-	<0.001**	-
	18.6 (11.4;26.3)	20.7 (13;29.5)	-	16.9 (11.3;28.7)	16.8 (12.1;28.3)	-		
Endurance, min	11.4 (6.53)	18.43 (9.17)**	16 (10.61)*	9.7 (5.12)	10.73 (6.83)	10.7 (5.83)	<0.001**	0.022*
	9.5 (4;27)	10 (3;32)	11 (3;32)	8 (4;24)	8 (3; 32)	9 (4;32)		
TUG, sec	7.6 (1.6)	6.9 (1.2)**	7.4 (2.2)	8.1 (1.7)	7.9 (1.7)	7.9 (1.9)	0.049*	0.838
	7.2 (5;11)	7.0 (5;9.5)	6.8 (5;13.5)	7.7 (5.5;13)	7.6 (5;11.8)	7.5 (5;13)		
STS, n	22.6 (4.2)	25.7 (5.33)**	25.1 (7.64)*	22.7 (5.49)	23.2 (5.65)	24.4 (5.47)*	0.004*	0.411
	23 (15;31)	26 (14;37)	26 (5;38)	23 (9;40)	24 (10;33)	25 (10;36)		
Isometric elbow	15.6 (5.6)	16.3 (5.6)	15.5 (5.61)	15.6 (6.32)	15.5 (6.17)	15.9 (6.7)	0.265	0.587
flexion force	14.9 (6.7;32.9)	15.3 (6.9;32.6)	15.5 (4.2;29.9)	14.6 (6.3;30.8)	13.6 (6.3;32)	14 83.2;31.6)		

* p>0.05 compared to week 0. ** p>0.001 compared to week 0. HAQ-DI: Health Assessment Questionnaire-Disability index; LTPAI: Leisure tome physical activity Instrument; PGIC: Patient global Impression of Change; VAS: Visual analogue scale; MFI: Multi-dimension Fatigue Inventory; HADS: Hospital Anxiety and Depression scale; ESAI: Exercise Stage assessment Instrument; CPET: Cardio Pulmonary exercise test; TUG: Timed Up and Go; STS: Sit to Stand test

4.2 STUDY II

Exercise with person-centred guidance decrease fatigue and symptoms of depression

The results in Study II show a significant improvement of the MFI-20 subscales Physical fatigue (p=0.002) and Mental fatigue (p=0.048), but no significant differences for the other subscales of MFI or VAS fatigue (Table 7). There was also a significant difference when groups where compared in the HADS depression subscale (p=0.039) with a decrease in the exercise group, but not in the anxiety subscale.

At the 12-month follow-up there were no significant differences when groups were compared (Table 7).

This study also included an analysis of metabolomics. Targeted analysis identified 146 unique plasma metabolites. Out of these metabolites, 17 were significantly associated with change of the MFI-20 subscale Physical fatigue and change in aerobic capacity. When groups were compared, decreased levels of the following metabolites were found in the exercise group: 1-myrstolyglycerol (p=0.001=, 24-methylcholesterol (p<0.001); cholesterol (p=0.046); campesterol (p<0.001); and α-tocopherol (p=0.003). Circulating levels of agmatine (p=0.027) and phenylpyruvic acid (p=0.020) were also increased in the intervention group.

Table 7. Between group analysis of change of the outcomes of Study II. Original table from publication [111] used with permission according to the Creative Commons Attribution 4.0 International License

	Intervention group n=36			Control group n=38			Between-group differences	
	Week 0	Δ 20-0 w	Δ 52-0 w	Week 0	Δ 20-0 w	Δ 52-0 w	20-0 w P-value	52-0 w P-value
MFI-20								
General Fatigue	8 (6.3-13.8)	-1 (-3-0)	0 (-3-1)	12 (9.3-13.8)	0 (-3-2)	0 (-2-2)	0.345	0.952
Physical Fatigue	9 (6-13)	-2** (-3- (-0.8))	-2* (-3.3-1)	10 (7.5-13.5)	0 (-1.8-2)	0 (-2-1)	0.002*	0.084
Mental Fatigue	8 (5-11)	0 (-1.3-4)	0 (-3-2)	9 (4.5-11)	0 (0-1)	0 (-1-2)	0.048*	0.466
Reduced Motivation	6 (4-9)	0 (-1-0.3)	0 (-1-1)	7 (4 -9.5)	0 (-1-2)	1* (-1-2)	0.106	0.156
Reduced Activity	9 (5.3-13)	-1* (-2-1)	-1 (-3-0)	11 (7-13)	0 (-1.3-2)	0 (-2-2)	0.074	0.095
VAS-F, 0-100 mm	26 (7.3-50.5)	-2 (-11.5-4.8)	-1 (-16-8)	28.5 (9.8-42)	0 (-11-11.8)	-3 (-10-17)	0.355	0.707
HADS (0-21)								
Anxiety	2.5 (0.3-6.8)	-1 (-2-0)	0 (-1-1)	2 (1-6)	0 (-1-1)	0 (-1-1)	0.064	0.370
Depression	2 (1-4)	0 (-1-0)*	0 (-1-0)	2 (1-4)	0 (-0.5-2)	0 (-1-1)	0.039*	0.328

*Significant difference, p<0.05, **Significant difference, p<0.001. Variables are presented as medians (IQR). MFI: Multidimensional Fatigue Inventory; VAS-F: Visual Analog Scale Fatigue; HADS: Hospital Anxiety Depression Scale.

4.3 STUDY III

Several aspects are experienced as influencing the transition to independent exercise

The qualitative interview study resulted in six categories with 21 subcategories.

A feasible opportunity to adopt exercise

The exercise with person-centred guidance was described as an opportunity to adopt to exercise through a person-centred introduction with adjustments and advancement making the exercise feasible even in the presence of some less positive elements such as some finding the exercise boring. The participants described experiences different from previous exercise experiences and some described themselves as fortunate to take this chance.

Experiencing positive effects of exercise

Exercise was described as positive and fun and giving a feeling of health. Positive effects manifested in everyday life and was both physical and mental.

Contextual factors affect the experience of exercise

To receive guidance from a physiotherapist gave a feeling of security and at the same time added to motivation by becoming a driving force for exercise. The arrangements of the exercise enabled both social group experiences and independent exercises, which were experienced as very different by different persons with some wishing for both more and less group arrangements. The facilities were also described as influencing the experience in both positive and negative ways.

Developing knowledge and thinking

The participants described that they gained knowledge about exercise performance and adjustments. They also described how their thoughts about exercise and themselves evolved and that the gym was conquered as a new arena.

Finding one's way

Among the participants there were descriptions of different ways of making the exercise one's own. Practicalities to fit the exercise routine in everyday life were described as were strategies to take on an exercise protocol, transit to independent exercise, and keep the motivation for exercise.

Managing barriers for exercise

Different barriers for exercise, such as reduced health or competing activities, were described as well as various strategies for overcoming these. Will power and determination were described as important.

4.4 STUDY IV

Physical activity level change over four years

The preliminary results of Study IV are presented in Appendix IV. There was no significant difference between groups, when change in physical activity level on LTPAI after four years was compared.
. However, there was a significant increase in weekly hours of physical activity within the intervention group when compared to baseline (Figure 4).

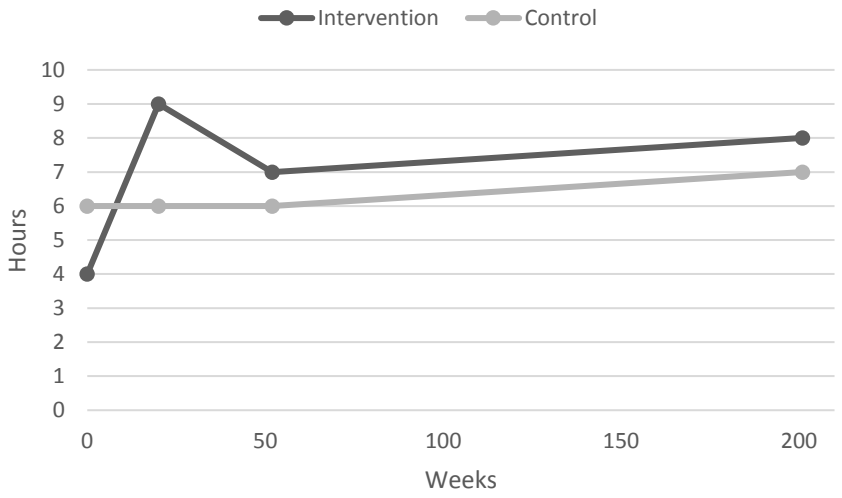

Figure 4. Change in self-rated physical activity over four years

There were no significant difference in change of physical fitness after four years when groups were compared.

There was a significant difference between groups when change of VAS global health ($p<0.05$) and number of tender joints ($p<0.05$) were compared between groups. Only within the control group there was a significant worsening of VAS global health, VAS pain, VAS fatigue, number of tender joints, and disease activity assessed with DAS 28 ($p<0.05$).

Three factors were found significantly ($p<0.05$) associated with increased physical activity after four years. Higher values of BMI, VAS fatigue and LTPAI at baseline were associated with a reduced probability of increased physical activity after four years.

5 DISCUSSION

Moderate- to high intensity exercise is beneficial for older adults with RA

The results of this thesis show that moderate- to high intensity exercise is beneficial for older adults with RA. Performing exercise with a person-centred guidance is experienced as manageable and could facilitate the transition to independent exercise. The main finding of this thesis is that physical fitness improves after partaking in exercise and this is accompanied with small but yet positive effects on fatigue and symptoms of depression. For older adults with RA, these are important findings since physical fitness decreases as one ages and due to RA (20, 147). Furthermore, because both fatigue and depression, which affect quality of life (148), are more common in persons with RA (40, 41, 149), interventions should target these symptoms.

There is strong evidence that physical activity and exercise helps maintain health and plays a part in disease prevention, especially as individuals age (3, 92, 150). This thesis supports the recommendation of exercise as part of the routine management of RA, (1, 2) also in higher ages. In addition, the participants rated their health as improved and found that exercise was fun and a positive addition to their lives and gave them a feeling of being health. That is, exercise resulted in positive effects manifested in their everyday lives. These experiences also strengthen the feasibility of incorporating such recommendations into practice.

The design of exercise-interventions matter

In the design of the intervention of Study I a person-centred approach was chosen to facilitate the introduction of exercise. A person-centred approach is suggested to increase self-efficacy (151) and is suitable to introduce exercise in persons suffering from pain (11). In Study III, the participants described the exercise intervention as increasing their self-efficacy and a personal development was described as being important for managing the transition to independent exercise. This finding supports the assumption that the person-centred design influenced the results in this study.

All participants in the exercise group completed the intervention. This fact seems to support the idea that the design of the intervention helped the participants cope with their needs and adverse events. The participants also expressed that their physiotherapist provided them with knowledge about how to properly perform exercises and a sense of security about participating in exercise. Several of the applied physiotherapist practices has been

acknowledged to help change physical activity behaviour: gradual increase of intensity, physical activity plans based on goals, close instructions when needed, and encouragement of progress (152).

Self-management, is hard to maintain, but an established relationship between patients and physiotherapists can facilitate self-management and motivation for self-management (108). Therefore, the follow-up phone calls the physiotherapists made might have contributed to the high level of maintaining exercise during the first year of the study.

Long-term maintenance of exercise is difficult

For older adults, interventions seldom succeed in increasing physical activity level for more than six months (153). Although knowledge on how to best promote maintenance of exercise is insufficient (154, 155), few studies have followed exercise over a long time. Several studies have examined strategies that change exercise behavior to adopt to exercise (96, 99, 152) and several techniques, including goal-setting and social support, have been suggested (152).

Based on the known challenges of physical activity maintenance (156), the results are good from Study I, where exercise was maintained with both good intensity and frequency, for a large part of the exercise group for the first seven months after the intervention. Study III also supports that the intervention prepared the participants to continue with exercise and to manage barriers. After four years, no significant differences in physical activity were found when groups where compared, which was an expected result based on previous findings (157). Continuous support could have contributed to maintaining higher levels of physical activity (108, 146) in the long term. Even with long-lasting support, upcoming barriers might be impassable for older adults (158).

However, the with-in group analysis of Study IV might indicate that previous experience with exercise could contribute to a long-lasting small increase of physical activity with-in the exercise group. As dose-response relationship exists between physical activity and health benefits, even a slight increase of physical activity can mean gains in health status (159) and even light intensity physical activity reduces occurrence of cardiovascular disease (160). Further studies are needed to evaluate if interventions with person-centred guidance from a physiotherapist, is important for increased physical activity over several years.

Positive results for cardio metabolic health parameters could be found as long as ten years after an exercise period (161) highlighting the importance of performing physical activity and exercise, even if it is not maintained for a long time. Maybe this could explain the worsening of self-rated global health found among the control group but not in the exercise group after 4 years.

METHODOLOGICAL CONCERNS

The participants of all four studies in this thesis were collected from the same recruitment. Before inclusion to Study I a power calculation was performed. However, the number of included subjects were small when it came to the metabolomics analysis. The analyses in Study IV might also have gained from including more participants and a more ample regression analysis containing more variables would have been possible. With screening of more than 1000 medical records, considerable efforts were made to include as many subjects as possible. For future studies, a design that offers the intervention at several locations so subjects living far from the site can participate or even inclusion of more sites might be necessary to recruit larger samples for this type of study. As serious co-morbidities served as exclusion criteria, many persons were excluded since the risk for co-morbidities increases with age (50). Exercise studies including persons with sever co-morbidities needs to be performed with in specialised health care.

The inclusion processes resulted in problems recruiting adults above the age of 75; very few of the invited persons accepted participation and the few who did were excluded due to heart conditions. This resulted in the sample limited to 65-75 year olds, so the results might not be transferable to older persons. It has been argued that the definition of 'older' needs to be revised due to increase in human life expectancy (162) to above approximately 70 years or older based on life expectancies in Sweden (163) or even 75 years of age (16). Such a change would make our study population of the 'pre-old age' category. However, with RA leading to premature immune aging (48) and 65 years being the current age for retirement in Sweden, the commonly used definition of 65 years and older was selected. The recruitment processes bring that the results of the thesis are only valid for persons in the age span 65-75 years and with a low disease activity or in remission. Today, however, the treatment target for RA is remission and a vast majority reaches this goal (164). When comparing disability assessed with HAQ-DI between our population and 600 Swedish persons aged 65-75 with RA reported in the Swedish Rheumatology Quality register 2015, the mean value is 0.5 in both groups (165), which corresponds

to other study findings (166) and supports our findings as valid for a wide population.

Study I had a low drop-out rate and the participants could be suspected to be interested in and motivated for physical activity and exercise. It has been found that thoughts on the benefits of exercise is higher among persons with RA recruited to exercise studies than those not recruited and that fatigue is higher in those not recruited (167). Since motivation and positive expectations are important parts in successful adoption to exercise (73, 168), these factors need to be considered when recommending physical activity and exercise to older adults with RA in a clinical setting. A person-centred approach could facilitate such considerations.

The primary outcome HAQ-DI showed floor-effects and the responsiveness is low in the normal functioning range (115, 116). The selection, however, was based on the hypothesis that older adults with RA would be at double risk of disability and HAQ-DI is also generally used in RA trials despite known limitations (169) and it is part of the core set for outcomes in RA (170). For assessing fatigue and symptoms of depression, the selected outcome measures would have been more appropriate in a sample with a larger proportion of participants affected by a clinically relevant level of fatigue or depression.

In qualitative research, the concept of trustworthiness is of great importance for the quality of the work and meaning of the results (145). Trustworthiness refers to credibility, dependability, and transferability of results.

To establish credibility in Study III, data were collected during deep-interviews to ensure rich descriptions of the research question. Participants were also recruited from all study-groups and from both genders to grasp different perspectives, and participants who had different outcomes of the transition to independent outcomes were included. To address dependability, the research team openly discussed the study process, keeping the research question in focus. The team members performed parallel analysis and agreed on the final result. Transferability refers to how the results can be transferred to other settings and groups. The selection of participants, as discussed above, could be comparable to other older adults with a low RA disease activity. However, they all share experiences from one particular exercise intervention. Through a distinctive description of participants and context the reader is offered the final decision on which results are transferable to a particular context.

The overall methodology of the thesis, containing both quantitative and qualitative methodology, is assumed to be a strength that gives a more

comprehensive picture of the subject in focus (171). Long-time follow-up studies of exercise are not commonly found, and with maintenance of exercise being a great challenge in physiotherapy, such studies could add important results (172). Long-time follow-up is important, especially in non-pharmacological randomised controlled trails and where self-reported outcomes are used and long-lasting symptoms need to be followed over time (173).

6 CONCLUSION

This thesis concludes that moderate- to high intensity exercise with person-centred guidance from a physiotherapist is beneficial for older adults with RA and is experienced as manageable and facilitating for the transition to independent exercise. This thesis supports the recommendation of physical activity as part of routine management of RA in adults above 65 years of age. However, maintaining exercise over several years is challenging.

7 FUTURE PERSPECTIVES

With a comprehensive exercise intervention as the basis for the conclusions of this thesis, it will be of importance from a pragmatic and clinical perspective to further evaluate which components of the interventions were most important for the positive results of the study. Study III provides some ideas about important aspects of the intervention to further evaluate. The participants mention the support from a professional as important, but the contact twice a week for 20 weeks might be possible to reduce without affecting outcomes. The person-centred contact might also be important for developing one's own way to exercise.

For future research, it will be of interest to perform moderate- to high intensity exercise studies for older adults than the participants in this sample or with a high disease activity to study disability and inflammation. With research questions formulated with special focus on depression or fatigue, it would be important to recruit patients with clinically significant symptoms.

It is of great interest for future physiotherapists and other healthcare providers to search for effective methods to facilitate lifestyle changes and maintenance of exercise over time. The results of Study IV are vague, but they awaken questions about whether this type of physiotherapeutic model based on a person-centred approach could facilitate increased physical activity over a long time. Study IV also awakens questions about whether one period of moderate-to high intensity physical exercise can delay age-related decline of physical function and disease-activity related factors over time among older adults with RA. These questions needs to be studied in larger samples.

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