Exploring physical function, activity, and sustainable delivery of first-line treatment for patients with osteoarthritis

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2023

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Series of dissertations submitted to the
Faculty of Medicine, University of Oslo

ISBN 978-82-348-0242-3

Cover: UiO.
Print production: Graphic center, University of Oslo.

Content

Acknowledgements

This thesis was made possible thanks to invaluable contributions from a number of people. I wish to express my sincere gratitude to all the people who have contributed and supported me throughout this project.

Especially, I want to express my sincere gratitude to my supervisors, Anne Therese Tveter, Hanne Dagfinrud and Kåre Birger Hagen, for their invaluable advice and support. I truly feel outmost privileged to have had you as my supervisors.

Anne Therese, besides your kindness, your enthusiasm, dedicated involvement and problems solving skills is truly inspiring. I am truly grateful for your ongoing advice and support on project-related and personal matters these years. Without your endless availability, encouragement and support it would have been impossible for me to complete this project.

Hanne, for me you are "mother supervisor". I thank you for believing in me when I started at NKRR. I thank you for sharing your immense knowledge and experience. Your ways of guiding me will continue to inspire me in years to come. You gave me ongoing support in line with a goal of this thesis. Your timely advice and encouragement always were given in perfect "dosages" to support and motivate me. I am forever grateful for your invaluable support and guidance.

Kåre Birger, even before you gave me a position at NKRR you inspired me to pursue a PhD through our several coffee meetings. I thank you for sharing your tremendous knowledge and experience, and for inspiring talks on research and life. In particular, I am deeply grateful that your wise and encouraging words built a foundation of confidence to complete the project.

I thank my co-authors, project co-workers and collaborators who all made important contributions. Anne Christie, my sincere thanks for your dedicated work on recruiting patients, and for sharing your experience and professionalism. Liv Rognerud Eriksson and Liv Skancke, I extend my sincere gratitude for your outmost positive attitude and for facilitating patient recruitment at your patient education courses. Karin Magnusson and Sella A. Provan, I thank you for your vital contributions to one of the manuscripts. I would like to extend my sincere thanks to the AktiWeb project group. The patient research partners at the Norwegian Rheumatic Association, Ole-Martin Wold and Knut Øderud, the collaboration with you was crucial for developing AktiWeb. Ole-Martin, I truly value our close collaboration which always was constructive, fun and motivating. Knut, my sincere thanks to you for your invaluable feedback and input in the development of AktiWeb. I would also like to express my gratitude to the Ågot Hamre and Sissel Syvertsen who more than willingly volunteered to contribute as peer-supporters. Camilla Fongen and Kristine Røren Nordén, your enthusiasm, dedicated contributions and ongoing advice and discussions throughout the project is highly appreciated. A special thanks to Kim L. Bennell, Rana S. Hinman and Rachel K. Nelligan for their invaluable contributions to the development and the manuscripts. I would also like to thank all the clinicians at Diakonhjemmet Hospital, REMEDY who contributed in the recruitment phase, your contribution is highly valued. Not least, I thank all the patients for participating in the studies.

I owe a sincere thanks to my colleagues at NKRR who all have created a highly competent, kind and generous working environment. My previous office mates, Trond Haugmark and

Gunnhild Berdal, I simply thank you for being yourselves. You are inspiring way beyond work-related matters, and you have strongly contributed to make the PhD course joyful. My later office mate, Emil Eirik Kvernberg Thomassen, I am truly grateful for our talks, and for your understanding and support when I was stressed and bewildered. The “old KOS group” of fellow PhD friends who all have achieved a PhD degree. Trond, Gunnhild Anne-Lene Sand-Svartrud, Tuva Moseng, Else Marit Holen Gravaas and Helene Lindtvedt Valaas. Besides sharing an endless number of coffees, I am deeply grateful for your support and caring, and for providing an arena to discuss the many personal and work-related challenges and achievements as a PhD student.

I thank my family and friends for taking interest in my work, and for your supportive understanding. Mum and dad, thank you for always believing in me, and for your unconditional support. My brother, Kenneth, for giving perspective and reminding me about other important things in life such a visiting my family in Bergen or golfing.

Carina, my deepest and outmost heartfelt thanks rightfully belongs to you! Throughout the PhD journey you have given limitless understanding and support. Without you taking care of our children Alida and Theo-Aleksander around the clock, it would have been impossible for me to spend all the long hours and efforts into the PhD project. Alida and Theo, although you often misunderstood whether I went for a jog or at job, you always showed understanding and motivated me by giving me a loving hug when a left and when I came home.

Langhus, July 2023

Kenth-Louis H. Joseph

Funding

The foundation Dam, Norway (previous ExtraFoundation) was the main financial funder of the work with this thesis. The data collections had finicial funding from different sources:

1) The data collection in the Musculoskeletal pain in Ullensaker STudy was made possible due to funding by the South-Eastern Norway Regional Health Authority Osteoarthritis Research Group, the Anders Jahre Humanitarian Foundation, the Dr. Trygve Gythfeldt and Wife's Research Fund, and the Norwegian Rheumatism Association Research Fund.

2) The methodogical study (Paper II) was financially supported by Diakonhjemmet Hospital AS as employer of the authors of the study. Accelerometers were acquired by financial support granted by the Klaveness Foundation.

3) The AktiWeb project (Paper III and IV) was funded by the foundation Dam, Health and Rehabilitation.

Institutional support was provided by The Norwegian National Advisory Unit on Rehabilitation in Rheumatology, Center for treatment of Rheumatic and Musculoskeletal Diseases (REMEDY) , Diakonhjemmet Hospital, Norway. Website and peer-support resources in the AktiWeb project was financially supported by the Norwegian Rheumatism Association.

Abbreviations

6MWD	6-minute walking distance
ACR	American College of Rheumatology
ACSM	American College of Sports Medicine
ActiveA	Active with Osteoarthritis
BCE	Before the Common Era
BOA	Better Management of Patients with Osteoarthritis
BORG RPE	BORG Rating of Perceived Exertion
CI	Confidence Interval
COSMIN	COnsensus-based Standards for the selection of health Measurement Instruments
CVD	Cardiovascular Disease
DMARD	Disease-Modifying Antirheumatic Drug
ESR	Erythrocyte Sedimentation Rate
EULAR	European Alliance of Associations for Rheumatology
GLA:D	Good Life with osteoArthritis in Denmark
HOOS	Hip Disability and Osteoarthritis Outcome Score
ICC	Intraclass Correlation
ICF	International Classification of Functioning, Disability and Health
IPAQ-SF	The International Physical Activity Questionnaire-Short Form
IQR	Interquartile Range
IRD	Inflammatory Rheumatic Disease
JIGSAW	Joint Implementation of Osteoarthritis guidelines in the West Midlands
JIGSAW-E	Joint Implementation of Osteoarthritis guidelines across Western-Europe
K-L	Kellgren-Lawrence
KOOS	Knee Injury and Osteoarthritis Outcome Score
MET	Metabolic Equivalent of Task
ml/kg/min	Milliliter per kilo per minute
MOSAICS	Management of OsteoArthritis In Consultations
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
MUST	Musculoskeletal pain in Ullensaker Study
MVPA	Moderate to Vigorous Physical Activity
NICE	National Institute for Health and Care Excellence (UK)
NRS	Numeric Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drug
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
PA	Physical Activity
PARE	People with Arthritis/Rheumatism across Europe (in EULAR)
PWV	Pulse Wave Velocity
RCT	Randomized Controlled Trial
REC	Norwegian Regional Committee for Medical and Health Research Ethics
RF	Rheumatoid Factor
SD	Standard Deviation
SF OA	Synovial Fluid signs of OA
SMD	Standardized Mean Difference
VO2max	Maximum Oxygen uptake
VO2peak	Peak Oxygen uptake

List of Papers

I. Joseph KL, Hagen KB, Tveter AT, Magnusson K, Provan SA, Dagfinrud H. Osteoarthritis-Related Walking Disability and Arterial Stiffness: Results From a Cross-Sectional Study. Arthritis care & research. 2019;71(2):252-8.

II. Joseph KL, Dagfinrud H, Christie A, Hagen KB, Tveter AT. Criterion validity of The International Physical Activity Questionnaire-Short Form (IPAQ-SF) for use in clinical practice in patients with osteoarthritis. BMC musculoskeletal disorders. 2021;22(1):232.

III. Joseph KL, Dagfinrud H, Hagen KB, Nordén KR, Fongen C, Wold OM, Hinman RS, Nelligan RK, Bennell KL, Tveter AT. The AktiWeb study: feasibility of a web-based exercise program delivered by a patient organisation to patients with hip and/or knee osteoarthritis. Pilot Feasibility Stud. 2022;8(1):150.

IV. Joseph KL, Dagfinrud H, Hagen KB, Nordén KR, Fongen C, Wold OM, Hinman RS, Nelligan RK, Bennell KL, Tveter AT. Adherence to a web-based exercise program – a pre-post study among patients with hip or knee OA. *Submitted* January 2023.

Summary

Background: People with osteoarthritis (OA) represent a large and fast-growing patient group with chronic disease in need of life-long treatment and support to combat functional decline and comorbidities. Evidence-based treatment guidelines recommend patient education, exercise, and weight management as first-line treatment for all patients seeking healthcare due to OA. Exercise is medicine for OA, if exercise programs are prescribed in a specific dosage, adjusted to the individual patient. For this purpose, feasible and valid tools for measuring patients' physical activity habits are important. Long-term adherence to exercise programs is challenging, and patients' need for follow-up cannot be met solely within the healthcare system. Development of innovative and sustainable methods for delivery and support of exercise programs is therefore urgently needed. Patient organizations may be an unutilized resource, that may serve as a powerful source of support for patients in need of long-term adherence to exercise and may potentially play a role as an extension of the healthcare services.

Aim: The overall aim of this thesis is to contribute to development of feasible and sustainable management of patients with OA. The project has three research focuses: to explore physical function in OA patients, to assess the validity of tools for measuring habitual physical activity, and to examine the feasibility of and adherence to a web-based, peer-supported exercise program as part of treatment for OA patients.

Methods: This thesis comprises a cross-sectional, comparative study, a methodological study, and an experimental, single-arm, pre-post feasibility-study. In the cross-sectional, comparative study, physical function (6-minute walking distance, 6MWD) in OA patients was compared to a reference sample. In the OA sample, multivariate linear regression analysis was conducted to test for the association between 6MWD and arterial stiffness (Pulse wave velocity). Criterion validity of the International Physical Activity Questionnaire-Short Form was assessed, using an accelerometer (Actigraph) as criterion method. In the feasibility study, the innovative AktiWeb program was developed in collaboration with a patient organization, and comprised a website with patient information, a progressive aerobic exercise program, a digital exercise diary, motivational messages, and peer-support. Feasibility of the 12-week AktiWeb program was assessed in real-life, clinical setting, considering study logistics, patient acceptability and clinical outcomes (physical activity, cardiorespiratory fitness [VO2peak], and joint-related functioning, pain, disease activity, fatigue, self-efficacy and health-related quality of life). Adherence to the AktiWeb exercise program was evaluated and barriers for not completing the exercise sessions were mapped according to predefined barriers and free text.

Results: Patients with OA (n=479) had significantly shorter 6MWD than the reference sample (n=235). On average, women with OA walked 54 [535 vs. 589 m, 95% CI 36, 73] meters and men 49 [593 vs. 642 m, 95% CI 24, 74] meters less than their gender-matched peers. from the general population ($p<0.001$). The largest difference in walking distance was observed in the youngest patients aged 40-49 years. In the OA sample, 6MWD was inversely associated with PWV; 100 m longer walking distance corresponded to 0.3 m/sec reduction in arterial stiffness

(p=0.001). Patient-reported physical activity (IPAQ-SF) was weakly associated with objective accelerometer measures (rho 0.15-0.37). Patients under-reported total activity, walking/light activity, and sitting time, whereas they over-reported moderate to vigorous physical activity (MVPA). For patient-reported and accelerometer measured physical activity, 57% and 31% of patients achieved the recommended ≥150 minutes of MVPA per week, respectively. In AktiWeb, 71% of the patients consented to participate in the program, 90% returned a median of 11 exercise diaries (of 12 possible), and 73% returned questionnaire data at follow-up. The usability of the website was rated as "acceptable", 86% reported that the start-up exercise level was "just right", and 82% found that the exercise program was "quite easy/very easy" to understand. Due to the Covid-19 pandemic, only eight patients completed follow-up testing. Their MVPA increased by mean 16.4 minutes per day (p=0.005), and their VO2peak improved by mean 1.83 ml/kg/min (p=0.026). Among those completing follow-up questionnaires (n=22), 24-52% reported meaningful improvement across the different patient-reported outcomes. Half of the patients adhered to the exercise program (at least two exercise sessions a week for 8 to 12 weeks). Patients in the adherent group were significantly more active and had higher cardiorespiratory fitness than those not adhering. Sickness was the most frequently reported barrier for not completing the exercise sessions, whereas OA joint pain contributed to less than 10% of all reported barriers.

Conclusion: Patients with OA had significantly shorter walking distance than matched peers already from the age of 40, and walking distance was inversely associated with arterial stiffness, suggesting that walking ability is important for the CVD risk profile in patients with OA. Correlations were weak between patient-reported and objectively measured physical activity, and patients tended to under-report activity of lower intensity and over-report activity of higher intensity. A progressive web-based exercise program delivered by a patient organization was found to be feasible, acceptable, and safe in patients with hip and knee OA, with half of the patients adhering to the exercise program and improvements shown for physical activity, cardiorespiratory fitness, and several patient-reported outcomes. Half of the patients adhered to at least two exercise sessions a week for 8 to 12 weeks.

Summary in Norwegian

Bakgrunn: Artrose er en kronisk sykdom med stadig økende prevalens som for mange fører til betydelige smerter og funksjonstap. Evidensbaserte retningslinjer for behandling av artrose inkluderer pasientundervisning, trening og, hvis nødvendig, vektregulering som førstelinjebehandling for alle som søker helsehjelp for artrose. Trening er medisin for pasienter med artrose dersom treningsprogrammet blir foreskrevet med riktig dose og tilpasset den enkelte pasient, og dersom pasienten gjennomfører programmet. For å gi optimal tilpasning av treningsprogrammer som del av behandlingen, er det behov for valide og klinisk anvendelige instrumenter for måling av pasienters aktivitetsvaner. For å styrke etterlevelse av trening som behandling i den raskt voksende gruppen av pasienter, er det nødvendig å utvikle metoder og strategier for oppfølging utenfor helsevesenet. Pasientorganisasjoner og deres likepersons-nettverk er en viktig ressurs som potensielt kan fungere som en forlengelse av helsetjenesten.

Mål: Det overordnede målet med dette prosjektet er å bidra til utvikling av bærekraftig behandling og oppfølging av pasienter med artrose. Prosjektet har tre forskningsfokus: å undersøke fysisk funksjon blant pasienter med artrose, å vurdere validiteten av pasientrapportert fysisk aktivitetsnivå, og å undersøke gjennomførbarhet og etterlevelse av et web-basert, likepersonstøttet treningsprogram som del av behandlingen for pasienter med artrose.

Metode: Avhandlingen inkluderer en tverrsnittstudie, en metodestudie og en eksperimentell, en-armet, før-etter gjennomførbarhetsstudie. I den komparative tverrsnittstudien ble fysisk funksjon (6-minutters gangdistanse, 6MWD) hos artrosepasienter sammenlignet med en referansepopulasjon. Sammenhengen mellom 6MWD og arteriell stivhet (pulsbølgehastighet) ble i tillegg testet med multivariate lineære regresjonsanalyser i artrosegruppen. Kriterievaliditet for spørreskjemaet International Physical Activity Questionnaire-Short Form (IPAQ-SF) ble undersøkt ved å bruke akselerometer (Actigraph) som kriteriemetode. AktiWeb-programmet ble utviklet i samarbeid med Norsk Revmatikerforbund. Programmet bestod av en webside med pasientinformasjon, et progressivt treningsprogram med fokus på kondisjonstrening, en digital treningsdagbok, motivasjonsmeldinger og likepersonsstøtte. Gjennomførbarheten av det 12 ukers AktiWeb-programmet ble testet under reelle forhold i en klinisk setting, der vi undersøkte studielogistikk, pasientenes vurdering av programmet og kliniske utfall (fysisk aktivitet, kondisjon (VO2peak), leddrelatert funksjon, smerte, sykdomsaktivitet, tretthet, mestringstro og helserelatert livskvalitet). Videre ble etterlevelse av AktiWeb-programmet og barrierer for gjennomføring av treningsøkter kartlagt.

Resultater: Pasientene med artrose (n=479) gikk signifikant kortere på 6MWD-testen enn referansegruppen (n=235). Kvinner med artrose gikk i gjennomsnitt 54 [535 vs. 589 m, 95 % KI 36, 73] meter og menn 49 [593 vs. 642 m, 95 % CI 24, 74] meter kortere enn tilsvarende grupper i referanseutvalget ($p<0.001$). Den største forskjellen i gangavstand ble observert i den yngste aldersgruppen (40-49 år). I artrosegruppen var kortere 6MWD assosiert økt arteriell pulsbølgehastighet (100 m lengre gangavstand tilsvarte 0.3 m/sek reduksjon i arteriell stivhet, $p=0.001$). Pasientrapportert fysisk aktivitetsnivå (IPAQ-SF) hadde svak sammenheng

med objektiv akselerometer-basert måling (rho 0.15-0.37). Pasientene under-rapporterte totalt aktivitetsnivå, gange/lett aktivitet og stillesittende tid, mens de over-rapporterte moderat til anstrengende aktivitet (MVPA). Basert på pasientrapportert fysisk aktivitet oppnådde 57 % av pasientene anbefalingene om ≥150 minutter med MVPA per uke, mens 31% oppnådde anbefalingene basert på objektivt målt aktivitet. I AktiWeb samtykket 71 % av pasientene til å delta i programmet, 90 % returnerte i gjennomsnitt 11 treningsdagbøker (av 12 mulige), og 73 % returnerte spørreskjemadata ved oppfølgning etter intervensjonen. Websidens brukervennlighet ble scoret som "akseptabel", 86 % rapporterte at treningsnivået ved oppstart var "akkurat passe", og 82 % mente at treningsprogrammet var "ganske enkelt/veldig enkelt" å forstå. Grunnet Covid-19 pandemien var det kun 8 pasienter som fikk fullført testing av fysisk aktivitetsnivå og fysisk form ved oppfølgingstidspunktet. Blant disse økte i gjennomsnitt MVPA med 16.4 minutter per dag (p=0.005) og VO2peak med 1.83 ml/kg/min (p=0.026). Mellom 24% og 52 % rapporterte en meningsfull forbedring på de ulike spørreskjemaene (for leddrelatert funksjon, smerte, sykdomsaktivitet, tretthet, mestringstro og helserelatert livskvalitet). Halvparten av pasientene fulgte treningsprogrammet (minst to treningsøkter i uken i 8 til 12 uker), og disse hadde signifikant høyere aktivitetsnivå og kondisjon ved oppstart enn gruppen som ikke etterlevde treningsprogrammet. Sykdom var den hyppigst rapporterte barrieren for ikke å fullføre treningsøktene, mens artrose-relaterte leddsmerter utgjorde mindre enn 10 % av alle de rapporterte barrierene.

Konklusjon: Allerede fra 40 års alder hadde pasienter med artrose kortere gangdistanse enn alders- og kjønnsmatchet referanseutvalg. Sammenliknet med objektivt målt aktivitet, hadde pasienter med artrose tendens til å under-rapportere aktivitet med lavere intensitet og over-rapportere aktivitet med høyere intensitet, og en større andel ble vurdert til å fylle anbefalinger for aktivitet basert på selvrapportert enn målt aktivitet. AktiWeb-programmet ble utviklet og levert i samarbeid mellom pasientorganisasjon og helsepersonell, og ble vurdert til å være gjennomførbart, akseptabelt og trygt for pasienter med hofte og kne artrose. Halvparten av pasientene gjennomførte minst 2 treninger i uken i minst 8 uker.

1 Introduction

Osteoarthritis (OA) is a chronic disease of varying severity that creates a substantial disease burden for many patients. Globally, the already high number of people living with OA will continue to rise. There is no known cure for OA, and evidence-based treatment guidelines recommend patient education, exercise, and weight management as first-line treatments that should be offered to all patients with symptomatic OA. Strategies for long-term management are important to enable patients to maintain or improve physical function and physical capacity, as well as reduce the risk of developing comorbidities.

Hippocrates (460-370 BCE) is known to be the father of scientific medicine, and he was the first physician to provide a written exercise prescription [1]. In 2007, the American College of Sports Medicine (ACSM) launched a global initiative to mobilize healthcare professionals to promote exercise in their practice to prevent, reduce, manage, or treat diseases that affect health and quality of life in humans. The concept Exercise Is Medicine emerged from this initiative and laid the foundation for the current general recommendation of 150 minutes of exercise per week for healthy adults [1]. However, as part of *treatment* for patients, exercise must be prescribed in a specific dosage with regard to modality, intensity, frequency and duration, adjusted to the individual patient. For this purpose, feasible and valid tools for measuring patients' physical activity habits are important.

The long-term need for follow-up of the fast-growing group of OA patients cannot be met solely within the healthcare system, and alternative methods for delivery and follow-up of exercise programs urgently need to be developed. Patient organizations, with their established network of educated peer-supporters, may be an unutilized resource. The peer-support model is based on the belief that patients have a unique competence in supporting and motivating other patients and may serve as a powerful source of support for patients in need of long-term adherence to exercise, possibly playing a role as an extension of the healthcare service.

Although current recommendations for OA treatment include strengthening and aerobic exercise, health professionals most commonly implement strengthening exercises in treatment programs for OA patients. However, for optimal health benefits, OA patients should be offered exercise programs that also target the well-known general health effects of physical activity and aerobic exercise. There is growing evidence of an association between OA and increased risk of developing cardiovascular disease (CVD). Possible causes of this association are supposed to be inactivity due to OA-related pain and disability, as well as low grade

inflammation and use of non-steroidal anti-inflammatory pain medication. Although the causal mechanisms between OA and CVD are uncertain, there is a consensus that high intensity aerobic exercise can improve cardiovascular health and reduce the risk of developing CVD. A current challenge is that people with OA tend to have low levels of physical activity and adherence to prescribed exercise programs is sub-optimal. The development of innovative and sustainable methods for delivery, support, and follow-up of exercise programs is important to combat the negative consequences of chronic diseases such as OA.

The overall aim of this thesis was to explore factors that can contribute to developing feasible and sustainable management of patients with OA. The project has three research focuses: to explore physical function in OA patients, to assess the validity of tools for measuring habitual physical activity, and to examine the feasibility of and adherence to a web-based, peer-supported exercise program as part of treatment for OA patients.

Background

1.1 Osteoarthritis

1.1.1 Epidemiology – prevalence and risk factors

Global estimates suggest an OA prevalence of 10% in the adult population, comprising more than 300 million women and 200 million men affected by the chronic disease [2]. In the last few decades, the number of cases has increased by an estimated 128% for hip OA, 122% for knee OA, and 92% for hand OA. OA is a leading cause of years lived with disability [3]. This highly prevalent chronic disease not only affects the individual's function and health-related quality of life, it can also challenge the availability of healthcare resources and cause significant societal expenditures.

The description of prevalence and incidence vary depending on the population of interest and definition of OA (e.g., radiographic OA is more common than symptomatic OA) [4, 5]. In general, prevalence increases with age and OA is more prominent in women than in men [5-9]. Population-based studies from the UK, Sweden, and Norway have reported overall prevalence ranging from 13 to 53% [6, 8, 9]. Although OA was identified using different self-reported criteria in these studies, knee OA (7-31%) was slightly more prevalent than hip OA (6-19%) and hand OA (3-27%) [6, 8, 9]. OA may affect several joints, and the risk of multi-joint affection is reported to increase with age [8].

In addition to age, which is considered the primary risk factor for OA, and predisposition among women [10, 11], there is evidence for systemic risk factors, including genetics, obesity, metabolic syndrome, and bone health, and for joint-related risk factors, including joint shape and malalignment, injury, and muscle strength [11]. With increased aging and obesity in the general population, the prevalence of OA is expected to continue to increase in the years to come [12, 13]. This will not only result in a large proportion of individuals with OA-related disability, but also impact the societal costs related to loss of work productivity (e.g., disability benefits and sick leave) and healthcare expenditures [14-17].

In addition, lifestyle-related comorbidities, such as CVD, which may be associated with OA [18], are likely to add to the need for healthcare and socioeconomic costs. An increased need for healthcare services must be expected in the years to come [9, 19], and identifying cost-effective

ways to target modifiable risk factors can potentially contribute to curbing or decreasing the healthcare needs and costs.

1.1.2 Definition, diagnosis, and classification criteria

OA is described as a heterogenous joint disease involving anatomical and physiological aspects, as well as pro-inflammatory pathways. In 2015, the Osteoarthritis Research Society International (OARSI) endorsed this definition of OA:

"*Osteoarthritis is a disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodeling, osteophyte formation, joint inflammation and loss of normal joint function), that can culminate in illness.*" [20].

This broad definition was proposed to facilitate advances in the field of OA, including improvements in the diagnostic criteria, classification, and treatment.

OA may be diagnosed using different criteria in which joint pain is a focal symptom criterion. In the mid-1980s and early 1990s, the American College of Rheumatology (ACR) developed different clinical classification criteria for hip, knee, and hand OA [21-23] (**Table 1**). These criteria, however, were mainly designed to discriminate OA from other rheumatic diseases and to standardize the reporting of OA in research. In 2014, simplified diagnostic criteria were developed by the UK National Institute for Health and Care Excellence (NICE) (**Table 1**) with the aim of feasible diagnosis of OA in clinical practice. Parson and colleagues compared the agreement between radiographic, clinically reported, and self-reported knee OA in 395 adults [24]. In those with self-reported or clinically diagnosed OA, 72% and 66% had radiographic OA, respectively. Furthermore, 58% of those with radiographic OA did not self-report OA or were clinically diagnosed [24]. A recent study, found that the NICE criteria performed better than the ACR criteria and European Alliance of Associations for Rheumatology (EULAR) criteria (**Table 1**) in detecting patients treated in primary care due to symptoms or functional limitations related to knee OA [25]. The NICE criteria were also better in detecting those who self-reported doctor-confirmed radiographic OA [25]. This may imply that both self-reporting a doctor-confirmed OA diagnosis and using the NICE criteria are useful methods for categorizing patients in need of treatment due to OA.

In recent years, several imaging modalities, including magnetic resonance imaging (MRI), ultrasound, and radiography, have been used to study OA diagnosis and pathogenesis [26]. Radiographic diagnosis and OA severity are commonly scored using the Kellgren and Lawrence (K-L) classification system or the OARSI atlas. The K-L system is based on a global composite score of osteophyte formation and joint space narrowing ranging from 0 (no OA) to 4 (severe OA), where K-L grade 2 usually defines an OA diagnosis [27]. The OARSI atlas criteria is based on separate scores for several OA-related features, including osteophytes and joint space narrowing of the hip, knee, and hand joints, with established guidelines for defining OA [28, 29]. For both diagnostic and research purposes, a challenge regarding the K-L system is related to interpretation of the grading and variations in how the K-L grade 2 is applied to define OA [30, 31]. Another challenge is the discrepancy between the K-L system and OARSI criteria in defining the presence of OA [32]. In general, imaging is recommended for individuals with atypical symptoms to confirm OA or aid in differential diagnosis, but it is not recommended as a clinical routine for those with typical OA symptoms [33]. In 2015, OARSI proclaimed the need for methods or criteria to detect the risk of the development and progression of OA [20]. Advances in imaging techniques and research on biomarkers may improve the diagnostic criteria and classification of different OA stages and OA phenotypes in the years to come [26, 34].

Table 1. American College of Rheumatology (ACR) criteria for the classification and reporting of OA, National Institute for Health and Care Excellence (NICE) clinical diagnosis criteria, and European Alliance of Associations for Rheumatology (EULAR) diagnosis criteria.

	ACR			**NICE**	**EULAR**
	Hip	***Knee***	***Hand***	***Hip and knee***	***Knee***
Clinical	Hip pain AND: - Age > 50 years - Internal rotation <15° - Pain on internal rotation - Stiffness	Knee pain AND at least 3 of 6: - Age >50 years - Stiffness <30 minutes - Crepitus - Bony tenderness - Bony enlargement - No palpable warmth	Hand pain, aching, or stiffness AND At least 3 of 4: - Hard tissue enlargement of 2 or more of 10 selected joints* - Hard tissue enlargement of 2 or more distal interphalangeal joints - Fewer than 3 swollen metacarpophalangeal joints - Deformity of at least 1 of 10* selected joints	Age ≥45 years AND - Activity-related joint pain AND - Either no morning joint-related stiffness or morning stiffness lasting <30 minutes	Age >40 years AND - Knee pain - Morning stiffness - Functional limitation AND - Crepitus - Restricted movement - Bony enlargement
Clinical and laboratory	Hip pain AND: - Internal rotation <15° - ESR ≤ 45 mm/hour OR Flexion ≤ 115° if ESR is unavailable	Knee pain AND at least 5 of 9: - Age >50 years - Stiffness <30 minutes - Crepitus - Bony tenderness - Bony enlargement - No palpable warmth - ESR <40 mm/hour - RF <1:40 - SF OA			
Clinical and radiographic	Hip pain AND at least 2 to 3: - ESR <20 mm/hour - Osteophytes (femoral or acetabular) - Joint space narrowing (superior, axial, and/or medial)	Knee pain AND at least 1 of 3: - Age >50 years - Knee stiffness <30 min - Crepitus AND - Osteophytes			

Abbreviations: ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; SF OA, synovial fluid signs of OA (clear, viscous, or white blood cell count <2000/mm^3).
*The 10 selected joints are the second and third distal interphalangeal, the second and third proximal interphalangeal, and the first carpometacarpal joints of both hands.

1.1.3 Etiology, pathophysiology, and symptoms

Even if OA is characterized by "*cartilage degradation, bone remodeling, osteophyte formation, joint inflammation and loss of normal joint function*" [20], the etiology and pathogenesis is not fully understood. After traditionally being described as a mechanical "wear and tear" disease, OA is now recognized as a joint disease with a complex pathophysiology [20, 35, 36]. The early onset and development involve mechanical, metabolic, and inflammatory factors affecting all structures of the synovial joints, though most commonly observed in the hip, knee, and hand joints. Being recognized as a complex heterogenic disease, identifying phenotype subgroups with relevance for clinical practice and phenotypes for early onset and progression is an ongoing research focus [20, 34, 37]. The identification of such phenotypes could be a step towards more differentiated and targeted treatment for improved prognosis [38].

Overall, pain and functional limitations are the most pronounced symptoms in OA [35, 39]. Another common symptom is joint stiffness, which usually occurs in the morning and after prolonged inactivity [37]. The stiffness usually resolves within minutes after movement of the joint [37]. Although the stiffness may be directly or indirectly related to the pathogenesis of OA, the systemic negative effect on body functions following relatively short periods of inactivity is evident at the cell and organ level, and regular activity can counteract such deterioration [40].

Pain symptoms in early OA are described as episodes of predictable sharp pain or other pain characteristics, often triggered by weight-bearing activity [41]. Later in the course of OA, the pain can become more persistent. In advanced OA, pain may evolve to being more constant, often accompanied by episodes of unpredictable and intense pain [41]. The intermittent, intense pain has been linked to inflammation, which may exacerbate symptoms, often characterized as flares, but the understanding of a flare is most commonly related to increased or prolonged pain [35, 37, 42, 43].

The development of OA symptoms over time is not straightforward; for example, the degree of structural changes does not necessarily reflect the experience of pain [35, 44]. In knee OA, factors such as age and multi-joint OA are associated with progressive symptoms, whereas features such as bone marrow lesions and synovitis are indicated to be drivers of pain intensity [35, 45]. However, the development and progression of OA symptoms is diverse. Evidence suggests that pain trajectories may be "mild, non-progressive", "progressive", "moderate", "improving", "severe, non-improving" [46]; or "marginal", "mild" and "moderate"

[47]. The usefulness of dividing OA into pain trajectories is currently uncertain, as translating symptom progression into differentiated or "personalized" treatment has not yet been achieved [45]. However, pain symptoms are perhaps the most common reason for seeking healthcare, and treatment largely focuses on managing pain, as well as maintaining or improving physical function.

1.1.4 Comorbidity and mortality

Comorbidity is prevalent in almost 70% of individuals with OA according to recent evidence from 42 studies included in a systematic review and meta-analysis [48]. The presence of comorbid conditions has been shown to contribute to worse pain and poorer physical function in hip and knee OA [14], which may potentially aggravate the total burden of the disease.

OA-related CVD has been of particular interest in recent years. The association between OA and CVD has been described as multifactorial and complex, as OA may be a direct or indirect cause of CVD [49, 50]. The association between the two conditions has also been suggested to be explained by shared common risk factors (e.g., physical inactivity, obesity, and arterial stiffness) [18]. CVD in OA populations is suggested to be substantial, with a prevalence of 35-38% according to two meta-analyses [48, 51]. In a meta-analysis of longitudinal studies, individuals with OA were more likely to develop CVD than those without OA (risk ratio 1.69, 95% CI 1.13, 2.53), but this was not the case for myocardial infarction or stroke [51]. The more recent meta-analysis revealed that stroke is a key CVD comorbidity associated with OA [48], which further demonstrates that the association between OA and CVD is not straightforward. One explanation for the association between OA and CVD may be reduced physical function. Evidence shows that overall mortality and CVD comorbidity are mediated through walking disability [52-54] and self-reported walking difficulty has been shown to be independently associated with an increased risk of a CVD event (adjusted hazard ratio 1.30, 95% CI 1.23, 1.38) [54].

Mortality in OA was put on the agenda in 2008, when Hochberg published a systematic review concluding with moderate evidence for excess mortality in OA [55]. Studies published after 2008 have reported mixed results [52, 56-60], and evidence from systematic reviews with meta-analyses have shown that OA is not associated with increased risk of all-cause mortality [61, 62]. However, several studies examining cause-specific mortality have reported an increased risk of CVD mortality [52, 56, 59, 61]. Nüesch and colleagues reported 71% more CVD-related

deaths among those with OA than the general population [52], and a meta-analysis by Veronese and colleagues reported a 21% higher risk of CVD mortality [61].

Overall, evidence shows that individuals with OA have an increased risk of developing CVD. Although the causal relationship between OA and CVD has not been fully untangled, one factor could relate to impaired walking ability causing low levels of physical activity, which in turn contributes to poor cardiovascular health and CVD [18].

1.2 Physical activity and fitness

1.2.1 Definition of physical activity and fitness

Physical activity is defined as any bodily movement that requires increased energy expenditure [63], and the role of regular physical activity to promote health and well-being is well established [64, 65]. The general health and fitness benefits of regular physical activity is illustrated in **Figure 1**.

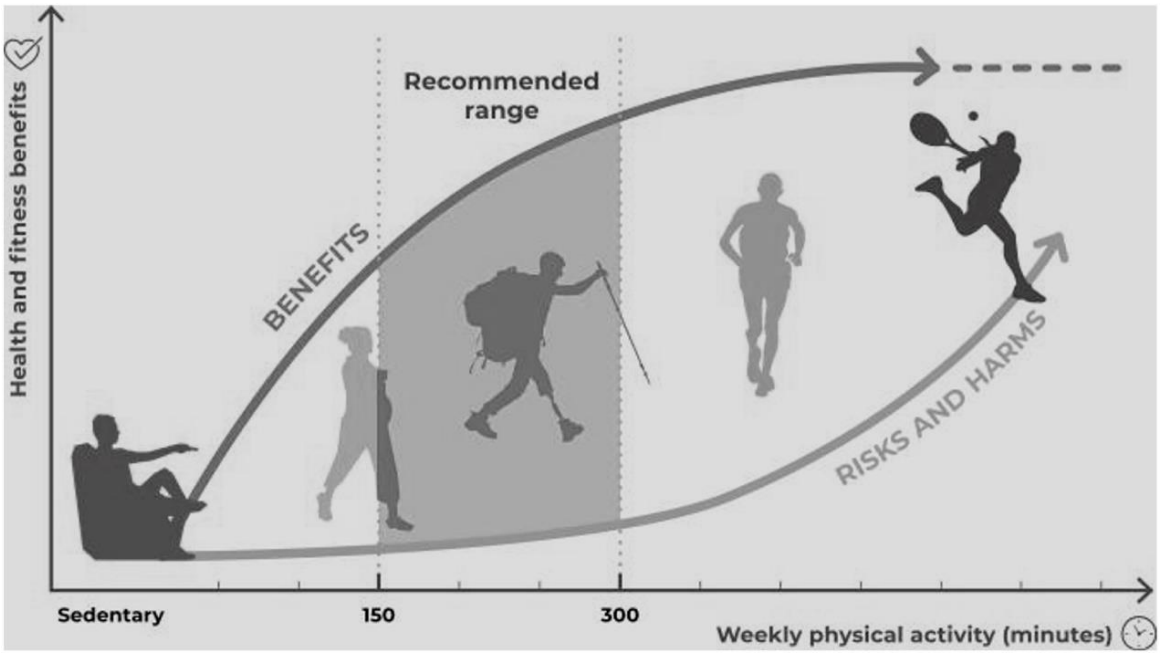

Figure 1. Illustration of benefits, and risks and harms of physical activity [64] (Licence: CC BY-NC-SA 3.0 IGO, color edited 27.12.2022)

The general health benefits of physical activity are supported by numerous large studies giving strong evidence that physical activity prevents a range of chronic diseases (e.g., CVD, diabetes, colon and breast cancer, obesity, hypertension, osteoporosis, depression) and premature mortality in the general population [66-71].

A dose-response relationship between physical activity and reduced risk of CVD is consistently reported [70-72]. Interestingly, a meta-analysis including more than one million individuals reported that higher levels of physical activity outweigh the risk of cancer and cardiovascular-related mortality associated with sedentary behavior [73]. Approximately 65-70 minutes of daily moderate activity was indicated to eliminate the mortality risk associated with a high amount of sitting time [73].

Physical activity behavior is related to physical function and physical fitness, i.e., a higher level of fitness can make participation in regular physical activity less strenuous due to increased capacity of the cardiovascular system, muscular strength, and endurance, and a fitness level below the requirements of daily living can reduce the ability to carry out daily tasks and participate in additional physical activity [63].

Though sedentarism poses detrimental effects on physical fitness, physical activity can, but does not necessarily, improve physical fitness [40, 74]. In order to improve fitness, the activity needs to be structured in a way that induces physiological responses [74]. Exercise is a subset of physical activity, and the widely accepted definition of exercise is activity that is "*planned, structured, and repetitive bodily movement done to improve and/or maintain one or more components of physical fitness"* [63, 74].

Physical fitness from a health perspective is often termed health-related fitness and has been defined as an individual's *"ability to carry out daily tasks with vigor and alertness, without undue fatigue, and with ample energy to enjoy leisure-time pursuits and meet unforeseen emergencies"* [63, 74]. Health-related physical fitness can be divided into four distinct physiological attributes [63] (**Figure 2**).

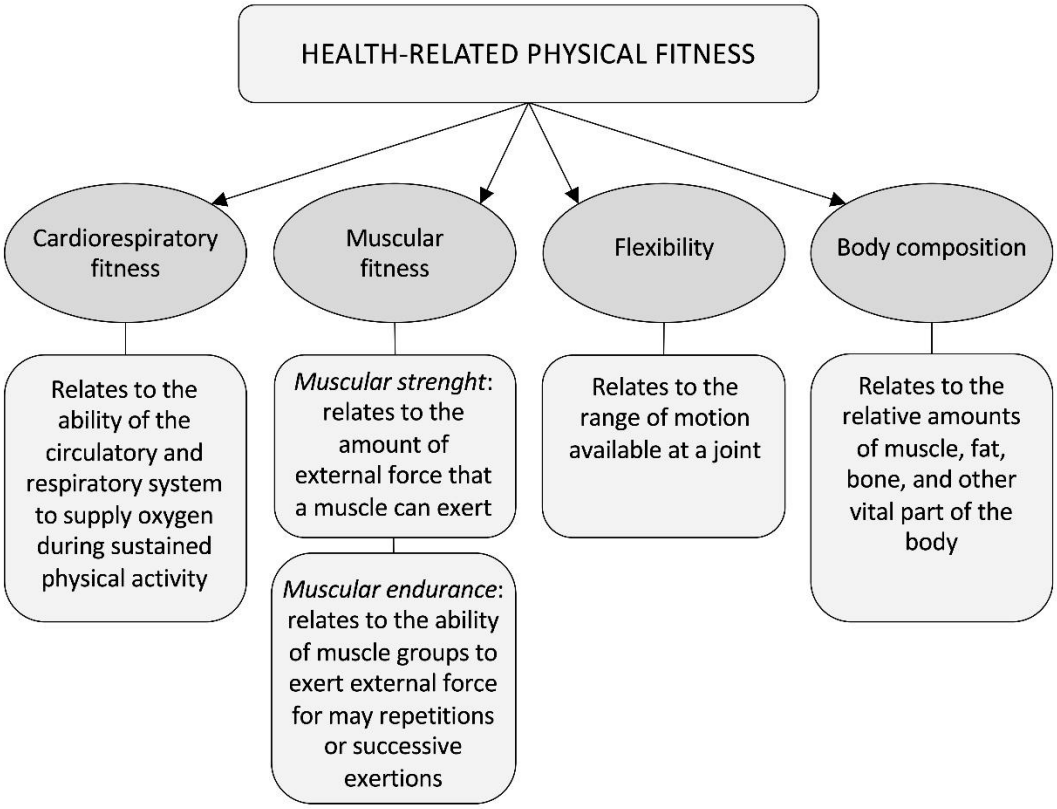

Figure 2. Physiological attributes included in health-related physical fitness [63]

1.2.2 Dose-response

The ACSM makes recommendations on how to assess physical fitness, as well as evidence-based guidance on how to prescribe exercise to maintain or improve physical fitness [74]. To improve physical fitness, the exercise dose needs to exceed the individual's current capacity or threshold. Exercise dose comprises frequency, duration, and intensity in terms of *how often, how long,* and *how hard* exercise is performed. The ACSM recommendations are based on a dose-response relationship between exercise dose and physical fitness (i.e., a higher exercise dosage results in higher fitness). Yet, in the concept *Exercise Is Medicine*, progressive stepwise increments in exercise dosage are needed. For example, to improve muscular fitness, the principle of *progressive overload* is recommended. Typically, 2-3 sessions per week with a gradual increase in repetitions and/or weight load is needed to improve muscular strength. To maintain muscular strength, as little as one session a week can be sufficient. To improve cardiorespiratory fitness, the principle of *start low and go slow* should be followed to reduce the risk of adverse events, as well as to enhance adoption and adherence to exercise [74].

Improved cardiorespiratory fitness is considered an independent protective factor for reducing CVD [75-77]. Due to the assumed increased risk of CVD associated with OA, individually tailored exercise programs to improve cardiorespiratory fitness are an important part of treatment. Therefore, adequate and feasible methods are needed in clinical practice to assess and monitor fitness and activity behavior.

1.2.3 Physical activity and exercise in OA patients

Some observational evidence indicates that many people with OA have low physical activity levels and tend to spend large amounts of awake time being sedentary (about 8-11 hours a day) [78, 79].

A meta-analysis of observational, cross-sectional, and experimental studies showed that only a small proportion of people with OA meet the minimum physical activity guidelines [80]. Among those with hip and knee OA, 13-60% met the guidelines when different criteria for determining fulfillment of the guidelines were applied. For example, in knee OA, 13-41% achieved 150 minutes of moderate to vigorous activity per week. Approximately half (48%) achieved 7000 steps/day, whereas only 19% achieved 10,000 steps/day [80]. One cross-sectional study included in the meta-analysis reported that only 13% of the men and 8% of the women achieved 150 minutes of moderate to vigorous aerobic activity in at least 10-minute sessions [81].

In a small observational study, physical activity and self-reported outcomes for pain, function, and quality of life were examined in a group of 60 patients who had undergone total knee arthroplasty and a group of 63 patients who later underwent total knee arthroplasty [82]. Although the patient-reported outcomes improved in the group that underwent arthroplasty compared to the group that later underwent arthroplasty, the activity level was similar in both groups, with an average of 12-13 minutes of moderate activity per day. Even though the post-surgery group improved in symptoms, less than 5% met the physical activity guidelines; thus, the authors concluded that specific interventions are needed to increase physical activity levels for these patients [82].

In a larger cross-sectional study, similarly low proportions met the guidelines. Liu and colleagues used data from 533 adults with OA who completed the US National Health and Nutrition Examination Survey (2003-2006) and reported that 3.5-14.8% met the activity guidelines according to activity monitoring measures [78]. The mean moderate to vigorous

physical activity was approximately 11 minutes per day but, interestingly, 53% self-reported as meeting the guidelines for physical activity levels [78].

Overall, evidence shows that many people with OA have low levels of physical activity, which can potentially cause or be the consequence of poor functional capacity. Having comorbidities (e.g., CVD, diabetes, back pain) in addition to OA is associated with worse pain and poorer physical function [14], often resulting in a vicious circle of less activity and more disease. Physical activity is known to be effective for preventing and limiting comorbidities, and reducing sedentary time has been shown to bring large health benefits [68, 83, 84]. Exercise is medicine for people with OA, and sustainable methods for the delivery and follow-up of exercise programs as part of their management program are urgently needed.

1.2.4 Measuring physical activity and fitness

Measurements are essential in health research and clinical practice [85]. In addition to being central in research investigating the effect of treatment interventions, accurate and reliable measures are important in the field of chronic diseases in order evaluate patients' health-related behavior, physical functioning, and biophysiological features [85]. Thus, valid measurements are crucial for providing tailored, progressive exercise as part of the treatment plan.

Instruments for measuring health-related features can be broadly divided into subjective and objective methods. Subjective instruments address a patient's own experience of health-related behavior or other health-related aspects, and the measure primarily relies on an individual's perception and judgement, whereas objective measures involve little or no judgement from the patient [85].

In the field of OA and other musculoskeletal diseases, instruments to measure physical activity, physical function, and fitness include a variety of objective and subjective methods [86-89]. Which instrument to use should mainly depend on the purpose, but practical aspects, such as cost, time resources, availability, and patient acceptability are also relevant considerations when selecting the appropriate measurement tool [85].

In general, subjective measures are more feasible and available, which is perhaps a reason for why they are applied more frequently in research settings than objective methods. Objective measures, such as laboratory and non-laboratory-based methods, usually require more resources and are assumed to be more accurate (**Figure 3**).

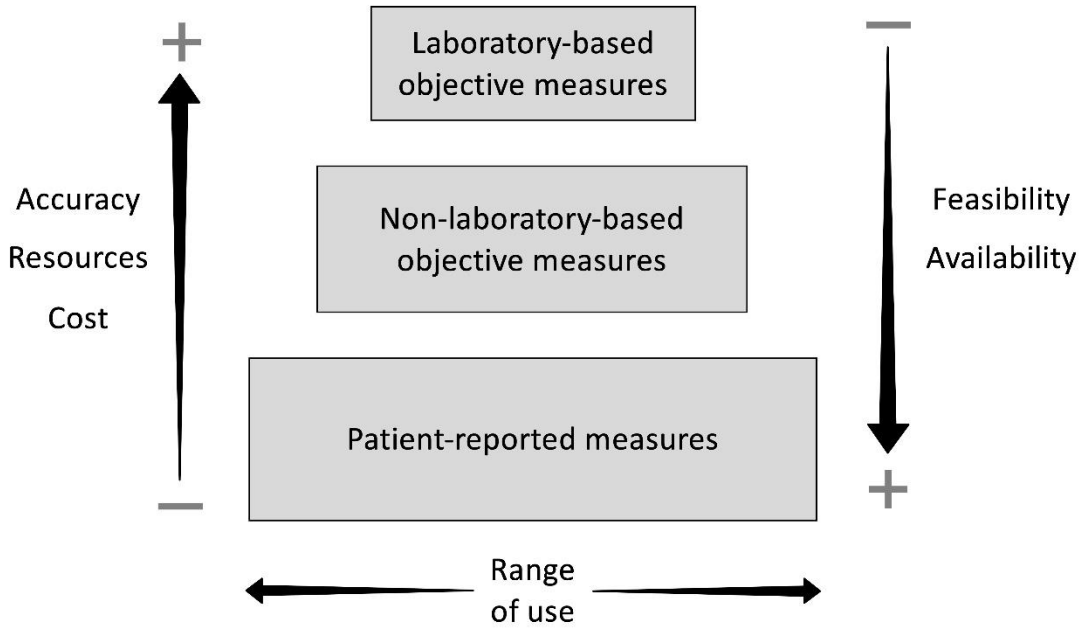

Figure 3. Illustration of the range of settings for the different measurement methods and their hierarchical qualities.

1.2.4.1 Objective measures of physical activity and fitness

In general, objective measures can be obtained with or without laboratory facilities. An example of a laboratory-based method is use of a treadmill and a mouth-placed tube connected to a computer to record a patient's carbon dioxide production and/or oxygen consumption. The principle of this method can be used to measure physical activity energy expenditure at defined workloads, and it can be used to measure cardiorespiratory fitness [74, 90].

Laboratory-based methods are usually considered "gold standard" measures [74], but they are restricted to a laboratory setting and are not appropriate to measure a patient's daily activity behavior or feasible for treatment purposes in large patient groups. For these purposes, other objective or subjective methods may be more appropriate.

Physical activity

Objective measures of physical activity in free-living environments include a variety of methods, such as the doubly labeled water method, heart rate monitors, and motion sensors (e.g., pedometers and activity monitors) [91, 92]. The doubly labeled water method is based on the intake of water comprising isotopes (hydrogen and oxygen) [91]. The elimination rate of the

isotopes is used to calculate carbon dioxide production and total physical activity energy expenditure, and requires laboratory-based analyses (i.e., mass spectrometry). Although the method is considered the gold standard for measuring the total energy expenditure during free-living physical activity, the method does not allow measurement of the structure or intensity of the activity [91]. Heart rate monitors and most motion sensors can give more detailed information about daily duration of intensity specific physical activity behaviors [92]. Heart rate monitoring is based on the linear relationship between heart rate and energy expenditure during activity, with the limitation that heart rate can be affected by other factors, such as medication or stress. Motion sensors primarily record a person's ambulatory movement, such as steps or acceleration of the body [92]. Numerous motion sensors exist, including different sensors that are based on accelerometry, usually termed accelerometers [87]. Accelerometers are small, noninvasive devices that can measure movement in one or more planes (e.g., the vertical and/or horizontal axis) [92, 93]. The principle of accelerometry is based on measuring the magnitude and frequency of body acceleration, indicating the muscular forces and energy expenditure behind the movement, which allows measurement of the frequency, duration, and intensity of physical activity [92, 93].

An advantage is that the objective measure is not influenced by the patient's memory or perception, as a person's physical activity is measured in real time, with the common caveat that objective measures lack information about context and type of activity. Another advantage related to heart rate monitors or accelerometers is the possibility of obtaining valuable information about the structure of habitual activity, which is important for health practitioners and patients as a basis for evaluating, tailoring, and progressing activity and exercise in their treatment program.

Physical fitness

Objective physical fitness measures that can be obtained outside the laboratory include physical performance and non-physical performance measures of different fitness components, such as functional muscle strength or cardiorespiratory fitness [86, 94-97].

Cardiorespiratory fitness can be measured by various methods, including maximal or sub-maximal physical performance methods (i.e., treadmill or cycle ergometer), and by non-performance-based calculations, all providing a measure of a person's maximal oxygen consumption, expressed as VO_{2max} or VO_{2peak} [74, 95, 96, 98]. In contrast to direct measures of respiration, these methods is used to calculate cardiorespiratory fitness, giving an indirect measure of fitness [74, 95, 96, 98]. Other physical performance-based measures include so-called

field tests, involving the performance of "everyday tasks" (i.e., walking distance or number of chair-stands) [86] that provide measures reflecting physical function and physical fitness (e.g., performance on a 6-minute walking test can be used to predict cardiorespiratory fitness) [99].

Different physical performance-based measures depend, to a varying degree, on the physiological and functional state of the cardiovascular, respiratory, and muscular systems [74]. An advantage is that the measure can reflect a patient's ability to perform daily activities and engage in regular physical activity, which is valuable information when evaluating a patient's functional and physical status [74]. In addition, the measures can support tailoring of exercise programs and defining treatment goals [74, 86], potentially acting as motivation for the patients to follow an exercise program to improve one or more fitness components. A general caveat of objective measures may be the tendency towards a biomedical view, not taking the patient's experience with the physical activity or performance into account, which is an important consideration in patients with chronic diseases, such as OA.

1.2.4.2 Patient-reported measures of physical activity and fitness

Patient-reported methods are frequently used to collect information about physical activity and physical function [88, 89, 100, 101]. Methods for measuring physical activity include questionnaires, diaries, and activity logs, which can measure activity over very short to life-long timeframes [102]. Physical activity is described as "*an exceedingly complex health behavior characterized by multiple dimensions and multiple domains" [103]*. Patient reporting can potentially give information about all dimensions and domains, including the intensity, duration, and frequency of activity, as well as the type and context for the activity (e.g., walking in the park during leisure time) [102]. The patient-reported questionnaires are retrospective, often asking about activity in the last week, month, or year, making the measure dependent on the patient's ability to remember their activity. Diaries or activity logs can offer the possibility of reporting hourly or daily activity, which may reduce the risk of recall bias and improve the accuracy of the measure [102].

Patient-reported methods to measure physical fitness include various questionnaires addressing the different physical fitness components, such as asking about how a patient would score aerobic fitness compared to peers of the same age and gender [104-107]. In addition, a recently developed fitness calculator could potentially be used for self-reporting cardiorespiratory fitness [96, 108].

A general advantage is that patient-reported instruments can easily be distributed to patients as paper-based or web-based questionnaires. Patient reporting is often used in research to collect information from large patient groups, and the method can provide immediate information about general health, health behavior, and health-related fitness status, which may be valuable for health professionals in tailoring exercise as part of treatment programs. Disadvantages relate to the lack of relevance and interpretation of the questionnaires (i.e., patients may be reluctant or find it difficult to answer questions that are not perceived as relevant or important) [109-112]. Questions with difficult wording and/or response alternatives can be a challenge to understand and answer, making the accuracy and usefulness of the measure dependent on the health literacy of the patient [111, 112].

Overall, a wide range of methods for measuring physical activity and health-related fitness exist, but a consensus has not been established on which measures to apply when assessing, evaluating, and providing physical activity and exercise as part of the treatment program in OA. Identifying accurate and feasible measures to assess and monitor activity level and fitness status can contribute to improving the provision of tailored activity and exercise as part of the treatment.

1.2.5 Measurement properties

The COSMIN initiative (COnsensus-based Standards for the selection of health Measurement INstruments) has developed a taxonomy with terminology and definitions of measurement properties (**Figure 4**) [113].

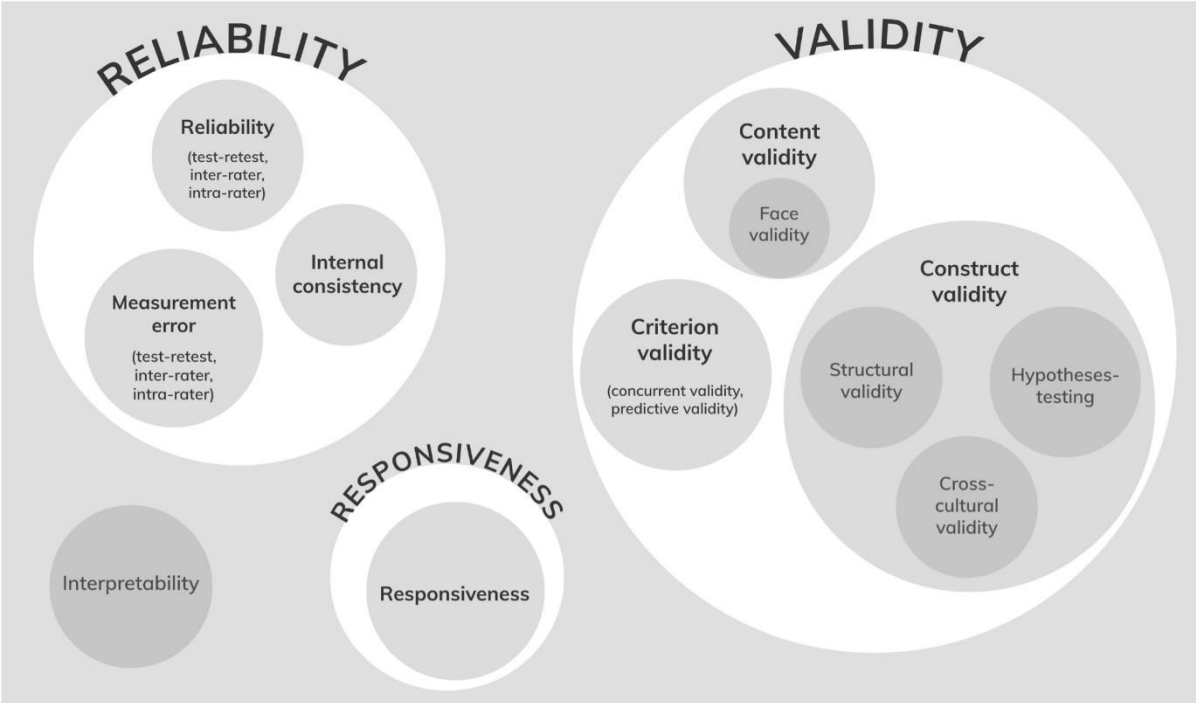

Figure 4. The COSMIN taxonomy of the measurement properties of outcome measurement instruments (retrieved from www.cosmin.nl, color edited 01.11.2022).

1.2.5.1 Validity

Three domains of measurement properties are presented separately for clarity purposes, but the properties "validity", "reliability", and "responsiveness" are closely related [113]. Validity refers to the degree to which an instrument measures the construct it intends to measure. Reliability plays an important part in evaluating validity in terms of the stability or degree of error associated with a measure. Responsiveness is often termed "longitudinal validity", referring to a measurement's ability to detect a change that is proportional to the change in the construct of interest. In the taxonomy, interpretability is not considered a measurement property, but denotes that interpretation is vital to understanding or giving meaning to a metric measure [113].

Validity comprises content validity, construct validity, and criterion validity [113]. Content validity refers to an instrument's ability to adequately reflect the construct of interest in the

target population, whereas construct validity refers to how well the measurement reflects the construct of interest. Criterion validity refers to the degree to which an instrument relates to the scores of a gold standard instrument [113].

Assessing the criterion validity of instruments can be particularly useful if new gold standard methods emerge or when using an instrument for another population than the one for which it was developed. Criterion validity can be divided into predictive and concurrent validity [85]. Predictive validity refers to how well measures of an instrument predict later outcomes, which are then evaluated by a gold standard method. Concurrent validity refers to the agreement between an instrument and a gold standard measure when measured simultaneously [85]. Assessing concurrent validity can be particularly useful when the construct of interest is related to complex behavior, i.e., when large day-to-day variations are common within and between individuals.

1.3 Management of OA

1.3.1 Biopsychosocial understanding of OA

The pathological disease progression characterizing OA can be regarded as an internal prosess, based on a biomedical understanding of disease. However, the well-known discrepancy between structural changes and symptoms (pain) in OA challenges a narrow biomedical understanding [44]. In contrast to the traditional biomedical perspective focusing on biological features to understand a disease, the biopsychosocial model recognizes that also psychological, social, and lifestyle aspects influence the disease course [114, 115]. Understanding OA-related pain from a biopsychosocial perspective means that the experience of pain may rely on an array of dynamically interwoven factors, such as pathological processes, mood, stress, sleep, exercise, occupation, education, and social support [116]. Current treatment recommendations refer to a holistic management approach, visualizing a present biopsychosocial understanding of OA [117-119]. The development of the AktiWeb project was based on a broad, biopsychosocial understanding of OA as a complex, multifaceted prosess requiring individual, patient-centred approach.

Maintaining or improving physical function is considered one of the most important aspects in the treatment of OA [120, 121]. Physical function is a term related to the degree of (dis)ability in performing daily tasks and activities [122]. The concept of physical function can perhaps be

best understood using the World Health Organization's International Classification of Functioning, Disability and Health (ICF) model [123]. The ICF model was developed to facilitate a standardized language to describe functioning across the spectrum of health conditions. According to this model, a person's functioning is reflected in the domains of 1) body functions and structures, 2) activities and participation and 3) personal and environmental factors [123].

The ICF model was used to develop the ICF core set for OA [124], which is a framework for classifying the typical spectrum of problems in OA-related functioning. According to this core set, OA can affect functioning under the domains of:

- Body functions (e.g., pain, impaired muscle strength, and reduced muscle endurance).
- Body structures (e.g., loss of cartilage tissue or muscle atrophy).
- Activities and participation (e.g., limited ability to walk and participate in recreational activities and social life).
- Environmental factors (e.g., lack of technology for use in daily living and health services, systems, and policies not meeting their healthcare needs).

These domains should be interpreted as interactive, mutually dependent factors and illustrate the broad and multifaceted aspects related to "functioning" in individuals with OA [124].

In a Delphi survey that reached consensus on the mandatory core outcomes in clinical trials involving patients with hip and/or knee OA, the survey members with OA ranked "mobility (such as walking)" as the most important aspect of physical function, followed by "self-perceived leg function", "self-care activities", and "sports, exercise and physical activity" [121].

1.3.2 OA treatment recommendations

Currently, no cure exists for OA. Hence, treatment recommendations focus on management strategies with the aim of curbing symptoms and maintaining or improving physical function and health-related quality of life.

In the last few decades, numerous recommendations and guidelines for the treatment of OA have been published. The development of recommendations is guided by standardized procedures to evaluate the quality of the evidence and emphasize consideration of beneficial effects against the potential harm of treatment [125, 126]. Different hierarchical illustrations of treatment recommendations have been published [127-129] (**Figure 5**).

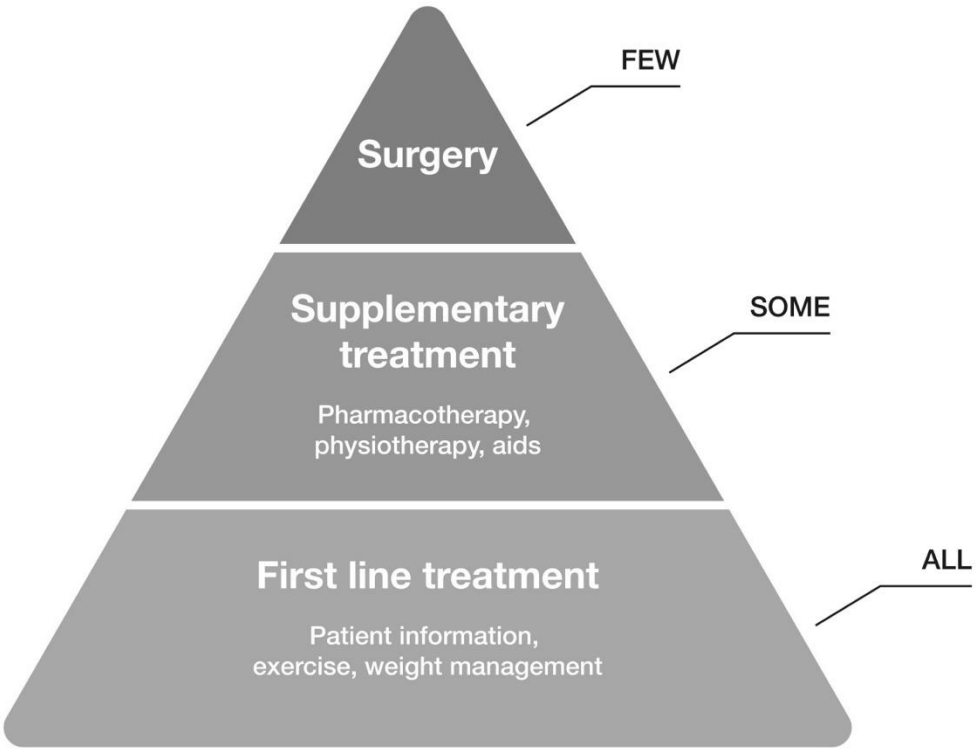

Figure 5. Treatment pyramid for hip and knee OA (printed with permission). The treatment pyramid illustrates that first-line treatment, including patient education, exercise, and weight management (if needed), should be offered to all patients, whereas some may need supplementary treatment approaches. Only a few patients may need surgery [130].

In a systematic review, Nelson and colleagues compared 16 different treatment guidelines published between 2003 and 2013 and concluded that there was broad agreement among them [131]. In 15 out of 16 guidelines, non-pharmacological treatment was recommended, and five main approaches were identified: 1) patient education and self-management, 2) exercise and weight loss, 3) assistive devices, 4) alternative and complementary approaches, and 5) surgical interventions. Furthermore, 11 of the 16 guidelines recommended various pharmaceutical treatments. Paracetamol was consistently recommended as the primary pharmaceutical agent in symptomatic OA. Second-line pharmaceutical agents included topical non-steroidal anti-inflammatory drugs (NSAIDs) and oral NSAIDs, with appropriate risk stratification and employment of gastroprotective strategies. Moreover, 6 of the 16 guidelines included surgical recommendations. Joint replacement was recommended for appropriate patients with knee or hip OA. The authors' summary of the non-pharmacological treatment recommendations was that all patients should be offered patient education and self-

management programs, be advised to exercise, and be advised to lose weight if overweight [131].

More recent guidelines reinforce previous recommendations for non-pharmacological first-line treatment, all recommending self-management, education, and exercise as first-line core components in the treatment of OA[117, 119, 125, 126]. Recent guidelines are more restrictive than previous guidelines on recommending paracetamol [125, 126, 131]. The most recently updated NICE guidelines, published in October 2022, make recommendations against routinely use of paracetamol and convey that there is no strong evidence of a benefit of using paracetamol [132]. In general, the most recent guidelines recommend that, if using pharmaceutical agents to manage OA is necessary, they should be used alongside first-line core treatment but at the lowest effective dose for the shortest duration possible [125, 126, 132].

Importantly, Nelson and colleagues underlined the strong agreement among the guidelines that general physical activity is important for managing OA and claim that health practitioners could use the physical activity guidelines for healthy adults as a basis for their recommendations [131]. This is supported in the recommendations from the EULAR task force for physical activity in people with inflammatory arthritis and OA, concluding that the public health recommendations for physical activity are applicable for people with rheumatic and musculoskeletal diseases, including OA [133]. The task force group commended that the general physical activity guidelines, including resistance and aerobic exercise, should be an integral part of standard care in hip and knee OA [133].

In the OA treatment guidelines, an overarching principle is that individuals should be involved in their own treatment strategy, emphasizing shared decision-making and individually tailored treatment approaches to ensure that the treatment strategy is agreed upon and according to the individual's needs [118, 119, 125, 126]. Most guidelines also agree that a combination of non-pharmacological and pharmacological treatment may be appropriate for some patients [119, 125, 126].

In summary, recommendations for the management of OA are consistent, with a common focus on patient education, exercise and physical activity, as well as weight management if needed. Pharmacological, surgical, and other management approaches should be considered as adjunctive to first-line treatment. [119, 125, 126, 131].

1.3.3 Evidence for treatment components

1.3.3.1 Patient education

Patient education for people with chronic diseases was introduced by the World Health Organization already in 1998 and, in line with this, patient education is considered standard care in OA management programs [125, 134, 135]. Patient education has been defined in different ways but can be broadly understood as information that informs patients about their disease and how it can be managed [135-137]. Patient education programs should comprise information that emphasizes "best practice" self-management strategies and approaches that enable the patient to make well-informed decisions to achieve the best possible outcome(s) [138].

The overall aim of patient education is to encourage positive health behavior in patients in order to maintain or improve long-term health outcomes [135]. However, solely providing patient education does not necessarily translate into more healthy behavior and improved health outcomes. A Cochrane review of 29 studies (randomized controlled trials (RCTs) or quasi-RCTs) assessing the effectiveness of educational programs for individuals with OA concluded that, compared to control programs (i.e., attention control, usual care), educational programs may, at best, slightly improve self-management skills, pain, function, and symptoms, though most likely without any clinical importance [139]. In another systematic review of 29 RCTs, Goff and colleagues reported that patient education alone or in combination with exercise improved pain and function compared to usual care [140]. However, they concluded that, even if patient education improved short-term pain and function, patient education should not be provided as a standalone treatment, but combined with exercise intervention [140].

1.3.3.2 Exercise

Extensive evidence supports the recommendations for exercise for individuals with OA. A wide range of interventions involving different types of exercise programs have been synthesized in numerous systematic reviews and meta-analyses, with outcomes often focusing on pain, physical function, and health-related quality of life [141-148]. In addition, two systematic reviews and meta-analyses concluded that exercise improves symptoms in individuals with OA, and that new trials are unlikely to change this conclusion [141, 148]. Yet, there is no consensus for when enough evidence has accumulated to be confident that "enough is enough", and studies examining different types and doses of exercise in different stages of OA could bring the field forward [149].

In the earliest review concluding that "enough is enough", Uthman and colleagues identified 66 studies published up until 2002 that evaluated the effect of exercise on pain and physical function compared to no exercise [141]. In this sequential analysis and network meta-analysis, the authors found that different types or combinations of exercise (i.e., strengthening or strengthening in combination with flexibility and aerobic exercise) was beneficial for pain and function. The majority of included trials were based on patients with knee OA. The authors stated that the most effective exercise management for lower limb OA was likely a combination of programs that improved strength, flexibility, and aerobic capacity [141]. The recent review stating that "enough is enough" included 42 trials on knee OA patients that examined pain reduction following exercise [148]. The authors reported that the effect estimates on pain reduction showed consistent results in studies with low risk of bias, and that subgroup analyses did not affect the overall effect estimate [148].

Two other Cochrane reviews evaluated the effect of various land-based exercise types and interventions, one including 10 RCTs of individuals with hip OA and one including 54 RCTs of individuals with knee OA [143, 144]. In the latter, high quality evidence from 44 trials showed that exercise reduced pain (SMD -0.49, 95% CI -0.39 to -0.59), moderate quality evidence from 44 trials showed improved physical function (SMD -0.52, 95% CI -0.39 to -0.64) immediately after exercise treatment, and high-quality evidence from 13 trials showed that exercise improved quality of life (SMD 0.28, 95% CI 0.15, 0.40) immediately after treatment [143]. Furthermore, a meta-analysis of 10-12 trials showed that the effects on pain (SMD -0.24, 95% CI -0.35 to -0.14) and function (SMD -0.15, 95% CI -0.26 to -0.04) were sustained 2-6 months after an exercise intervention. The authors concluded that land-based exercise provides a moderate benefit for pain and function in knee OA, and that the magnitude of the beneficial effect is comparable to reported estimates for NSAIDs [143].

The conclusion regarding comparable beneficial effects of NSAIDs and exercise was supported in a meta-analysis from 2016 [150]. The meta-analysis based on 54 trials (20 pharmacology, 34 exercise) from six different Cochrane reviews showed comparable beneficial effects on pain for pharmacological interventions (SMD 0.41, 95% CI 0.23, 0.59) and exercise interventions (SMD 0.46, 95% CI 0.34, 0.59). Further subgroup analyses on exercise types, analgesic agents, and patient characteristics did not reveal any differences between the subgroups. Notably, in these subgroup analyses, the lowest effect sizes were found for paracetamol and aquatic exercise, whereas the highest effect sizes were found for NSAIDs and land-based exercise [150].

In another meta-analysis, Juhl and colleagues included 48 RCTs published up until 2012 to identify the optimal exercise program for reducing pain and patient-reported disability in knee OA [142]. The results showed that aerobic (SMD 0.67, 95% CI 0.39, 0.94), strengthening (SMD 0.62, 95% CI 0.45, 0.79), and performance exercise (SMD 0.48, 95% CI 0.11, 0.85) resulted in similar significant improvement of pain compared to no exercise. Similar estimates were found for function. In addition, across patients with mild to moderate or severe OA, they found similar beneficial effects of exercise on pain and disability, though with less improvement in function among those with severe OA than those with mild to moderate OA. Interestingly, Juhl and colleagues reported that single-type exercise programs were more efficacious than programs combining different exercise types (SMD 0.61 versus 0.16, $p<0.001$) and concluded that the optimal exercise program should have one aim focusing on improved aerobic capacity, quadriceps strengthening, or lower limb performance [142].

Based on high-quality systematic reviews, we can conclude that there is a large evidence base supporting that exercise is beneficial to improve pain and physical function in individuals with OA [141-143, 148, 150].

1.3.3.3 Symptom-modifying mechanisms of exercise

Even if there is extensive evidence for beneficial health effects of exercise, the symptom-modifying mechanisms have not been extensively studied. Some evidence indicates that reduced muscle strength is associated with pain and disability in lower limb OA [151, 152]. Thus, the link between reduced pain and improved function with strengthening exercise is explained, at least in part, by increased strength in knee extensors [146, 152, 153].

The mechanisms underlying the symptom-modifying effect of aerobic exercise are less clear [142, 143, 154]. An intriguing explanation relates to the link between synovial-related inflammation and increased pain, including the evident (low-grade) inflammation in the pathogenesis of OA [36, 155, 156]. The acute anti-inflammatory effects of aerobic exercise, as well as the indirect anti-inflammatory effect of long-term exercise resulting in improved body composition, may explain the symptom-modifying outcomes after aerobic exercise interventions [157, 158].

As a theoretical approach to the anti-inflammatory mechanisms of exercise, Perandini et al. hypothesized that exercise can break the cascade of negative consequences in inflammatory autoimmune rheumatic diseases [159] (**Figure 6**).

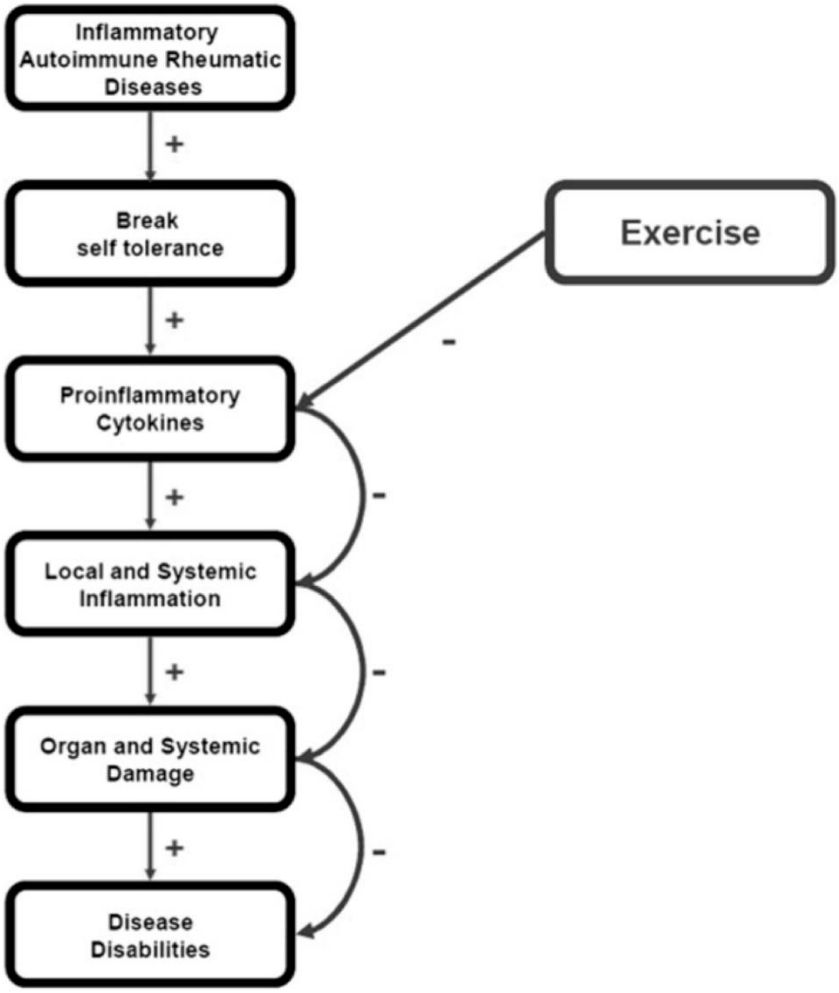

Figure 6. The hyphotezised role of exercise in inhibiting the inflammatory process and preventing inflammation in autoimmune rheumatic diseases [159] (Printed with persmission from Elsevier, color edited 27.12.2022).

Runhaar and colleagues included 94 studies in a systematic review and used mediator analysis to identify potential physiological explanatory factors for the relationship between physical exercise and improvements of pain and function [160]. They reported 12 categories of possible mediating factors: inflammation, cartilage or OA properties, muscle strength, muscle properties, range of motion/flexibility, gait properties, biomechanics, body weight/metabolic syndrome, bone properties, proprioception, (in)stability/balance, and aerobic capacity [160]. A scoping review of nine studies with mediation analyses examined the effect of non-surgical interventions on pain and function [161]. The authors concluded that some evidence suggests that improvements in pain and function are mediated through changes in body weight and systemic inflammation and self-efficacy (after diet and exercise), knee muscle strength and

self-efficacy (after exercise), and changes in self-efficacy (after high-expectation communication style) [161].

In a systematic review and meta-analysis focusing on knee OA, 45 trials (RCTs or quasi-RCTs) were included with the aim of examining whether strengthening exercises according to the ACSM guidelines differ from other types of exercise in regard to the effect on muscle strength, pain, and function [146]. A significant difference in knee extensor strength favoring interventions following the ACSM exercise guidelines was reported (SMD difference 0.448, 95% CI 0.091, 0.805; p=0.014), but the difference in effect estimates for pain and function was non-significant. In further analyses, the authors found that knee extensor strength is significantly associated with both pain and function but with large differences between studies. The authors concluded that an increase in knee extensor strength of at least 30% would be necessary to achieve clinical benefits in pain and function [146].

1.3.3.4 Weight control

Guidelines recommend weight loss for those who are overweight or obese [118, 119, 125, 126, 162]. In a meta-analysis of four RCTs, no clear relationship was found between weight reduction and pain in knee OA, but a weight reduction of more than 5% significantly improved function [163]. Similar results were found in another meta-analysis of nine trials in which the authors reported that an average weight loss of 10.5% after diet interventions did not reduce pain, but did improve function [164]. Furthermore, an average weight loss of 4.7% after interventions combining diet and exercise produced significant beneficial results for both pain and function [164]. In secondary analyses of an RCT of 240 patients with overweight/obesity and knee OA, Messier and colleagues found a significant dose-response relationship between weight loss and several outcomes, including pain and function [165]. Participants followed an 18-month dietary weight loss program alone or in combination with supervised exercise and were categorized into four groups based on the percentage of weight lost. Compared to <5% body weight loss, improvements in pain and function increased with weight loss of 5-10%, 10-20%, and >20%. The authors concluded that 10-20% weight loss provides substantial benefits compared to lesser weight loss [165].

In summary, clear evidence showing that diet-induced weight loss improves pain symptoms is lacking, but some evidence suggests that weight loss due to a combination of diet and exercise produces beneficial effects on pain and function.

1.3.3.5 Supplementary treatment and surgery

Supplementary treatment includes various types of pharmacological and non-pharmacological approaches that can be adjunctive to first-line core treatment. *Pharmacological treatment* includes several agents, of which paracetamol and NSAIDs are commonly recommended for periodic use with first-line core treatment [131, 132]. Results from a systematic review and meta-analysis of 13 RCTs showed that paracetamol has a small non-clinically meaningful short-term effect on pain and disability [166]. Another network meta-analysis of 76 RCTs reported that paracetamol had near to no effect on pain and concluded that paracetamol should not be used as single-agent treatment of OA [167]. The authors concluded that sound evidence supports beneficial effects on pain and function with periodic use of NSAIDs but that side effects associated with the drugs must be considered for each patient [167]. A later meta-analysis of 72 RCTs showed that the beneficial effect of NSAIDs on pain and function peaked at 2 weeks, after which the effect decreased over time, along with an increase in cases with minor adverse gastrointestinal and cardiovascular events [168]. A report of several studies concluded that topical and oral NSAIDs provide equivalent beneficial effects on pain in knee OA, with fewer adverse events recorded for topical NSAIDs [169].

Non-pharmacological additional treatment includes numerous passive treatments (i.e., acupuncture, thermal therapy, transcutaneous electrical stimulation) and aids (i.e., walking cane, braces, kinesiotaping, lateral and medial wedged insoles) [126]. In general, the evidence base for additional non-pharmacological adjunctive treatments is smaller and often characterized by mixed results and/or poor research quality or little treatment effect compared to the evidence supporting first-line core treatment [125, 126]. *Surgical treatment* most commonly involves total joint replacement [170]. The patients who can benefit most from surgery in terms of pain and function are patients with the most severe radiographic joint damage [171, 172]. Yet, surgery is not a guarantee for eliminating symptoms, as many may still experience persistent pain even after surgery [173]. A recent meta-analysis of 20 studies (observational and RCTs) reported that higher body mass index correlated with worse physical function, and that better OA severity and physical function correlated with better physical function 12 months after total knee arthroplasty [174]. Evidence from another meta-analysis of five RCTs showed that the potential beneficial effect on function and pain following surgery can be enhanced by pre-operative treatment comprising progressive strengthening exercise [175].

1.3.4 Current OA management programs

A handful of OA management programs have been implemented in healthcare practices in several countries with the aim of providing structured, high-quality, first-line treatment according to guidelines [176].

The UK-based "Management of OsteoArthritis In Consultations" (MOSAICS) study is an initiative that has led to international dissemination of OA treatment guidelines [177]. The MOSAICS study was a cluster randomized trial designed mainly to implement the NICE guidelines into primary healthcare by using a 'model OA consultation' design [177]. The MOSAICS intervention was based on several theoretical frameworks, including psychological theory frameworks for behavior change interventions [177-180], and included training in practitioner consultation skills and delivery of the intervention [177].

The concept of the MOSAICS trial was later used as a framework in the "Joint Implementation of Osteoarthritis guidelines in the West Midlands" (JIGSAW) and the international "Joint Implementation of Osteoarthritis guidelines across Western-Europe" (JIGSAW-E) projects. The JIGSAW-E project currently focuses on disseminating four key elements into healthcare practices across seven European countries (Norway, Denmark, Portugal, France, Scotland, the Netherlands, and UK): 1) patient information, 2) quality indicators, 3) clinician training, and 4) clinical system templates. The ongoing web-based dissemination of these four elements is meant to encourage healthcare practitioners to proactively support patients' self-management.

Other management programs aiming to deliver first-line core treatment are the "Better Management of Patients with Osteoarthritis" (BOA) program, the "Good Life with osteoArthritis in Denmark" (GLA:D®) program, the "Active with Osteoarthritis" (ActiveA), developed in Sweden, Denmark, and Norway, respectively.

The BOA program was initiated in Sweden in 2008, comprising education in evidence-based treatment for healthcare practitioners and a "minimum intervention" comprising two patient education sessions and a tailored strengthening exercise program with the main aim of supporting patients' self-management [181]. The tailored exercise program is mainly delivered by physiotherapists who provide a one-to-one introduction session, tailored support, advice, and individual adjustments twice a week for 6 weeks. The exercise program is performed in groups led by a physiotherapist, but the patients can also perform the program at home [181]. In BOA, the exercise program is not specified, but follows biomechanical principles (alignment

of hip-knee-ankle and good neuromuscular control) to ensure proximal muscle strength in the lower limbs [181, 182].

The concept of the BOA program was later adopted to develop the Danish GLA:D program, in which physiotherapists are educated and certified to provide the program [183]. The "minimal intervention" comprises two to three patient education sessions in addition to a group-based supervised neuromuscular exercise program delivered twice a week over 6 weeks [183-185]. Participants are encouraged to participate in supervised exercise to ensure an appropriate exercise level and progression [183]. The GLA:D concept has been adopted in Australia, Canada, China, and Switzerland [186].

In Norway, the BOA and GLA:D programs inspired the establishment of the ActiveA program, which is based on three pillars: education and certification of physiotherapists, patient education, and an exercise program to support self-management [187]. The ActiveA "Osteoarthritis School" comprises a 3-hour patient education course and supervised neuromuscular and strength exercise program delivered over 6-12 weeks that should be performed at least twice weekly [187, 188]. Physiotherapists provide exercise instructions and guide the dosage and progression of programs [187].

In general, the BOA, GLA:D, and ActiveA programs support continued physical activity and exercise by offering ongoing encouragement throughout the program, as well as at 3-month follow-up consultations. In addition, all initiatives include a national quality register including patient-reported data from patients participating in the program [181, 183, 187]. In addition to educating healthcare practitioners and providing patient education, these programs also provide evidence-based, tailored, and supervised strengthening exercise programs, which can be important actions to facilitate uptake and adherence to exercise as part of long-term self-management [189].

The current management programs with supervised follow-up can promote adherence to exercise, but providing long-term support with supervised exercise to a large and growing patient group is beyond the available healthcare resources. Developing sustainable programs to support patients with their long-term management can potentially reinforce current management programs, and produce beneficial long-term health outcomes for more patients.

1.4 Development of OA management programs

1.4.1 Framework for complex interventions

Development of OA management program should be guided by a complex intervention framework [139, 176]. "Complex intervention" is not clearly defined, but an intervention can be considered complex if it comprises several interacting components, several actions required by those delivering and those receiving the intervention, several settings, multiple stakeholders, various outcomes, and the need for *tailoring* rather than *standardizing* components in the intervention [190].

Several complex intervention frameworks exist, providing guidance on the development of programs prior to taking on a full-scale study [191]. An example is the model of care framework, which is described as a guide to facilitate delivery of evidence-informed guidelines into healthcare practice [192, 193]. Recognizing the need to evaluate complex, non-pharmacological interventions, the UK Medical Research Council (MRC) framework was developed to aid researchers, funders, and decision-makers in applying appropriate methods in the development of complex interventions [190, 194].

The AktiWeb program (Papers III and IV) was developed according to the MRC framework launched in 2008 [190]. The framework has been updated more recently, but the four main phases of developing complex interventions presented in the first version were carried forward in the updated version [190, 195]. The four main phases are 1) development/identification of the intervention, 2) feasibility/piloting, 3) evaluation, and 4) implementation as illustrated in **Figure 7** [195].

The four phases are connected but do not need to follow sequentially [195]. A research program can start in any of the phases, and it is also possible to move back or forward to resolve any uncertainties with the intervention. Development of a complex intervention refers to the entire process, from the initial conception phase to the feasibility or piloting phase and evaluation phase [195]. The implementation phase is part of the development but can be evaluated according to other frameworks [195, 196]. In each of the development phases, six core elements, (shown in the center of **Figure 7**) should be considered to guide whether the interventions should stop, need to be adjusted or refined, or can move forward to the next phase (**Figure 7**) [195].

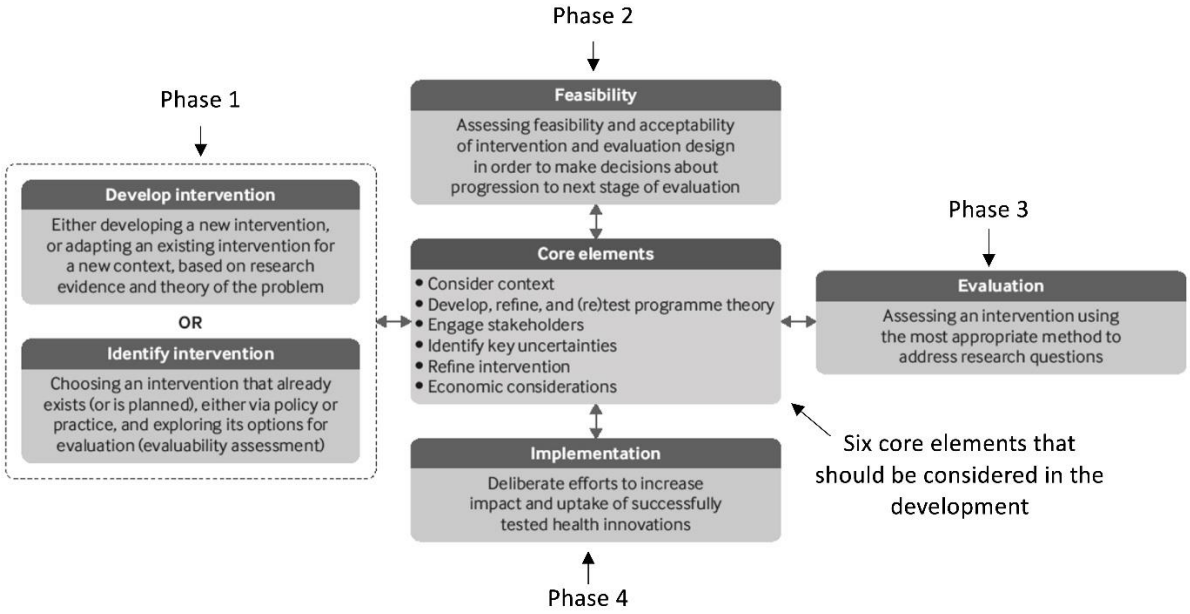

Figure 7. The four phases in the MRC framework for developing and evaluating complex interventions, including the six core elements that should be considered for each phase. (License: Creative Commons CC BY 4.0, color edited and added text outside the textboxes 06.12.2022).

When developing a complex intervention, the initial phase (Phase 1) refers to the process in which the intervention is *created and designed* [190, 195]. Building a complex health intervention relies on evidence-based "building stones", as well as health policy and practice-led perspectives [190, 195, 197, 198].

The *feasibility phase* (Phase 2) refers to conducting a feasibility study to assess and evaluate the feasibility and acceptability of the intervention [190, 195, 197]. A feasibility study is meant to gain information that contributes to reducing the uncertainty around logistics, including recruitment, data collection, and retention, as well as interventional uncertainties, e.g., content, delivery, and participant acceptability [195].

In the *evaluation phase* (Phase 3), research is set up to evaluate whether the intervention is effective with regard to the impact of the intervention and how it contributes to system change [195]. A process evaluation of the components that are delivered, how the intervention is delivered, and whether changes are produced can reveal what works, how it works, and why it

works, which in turn enables further optimization of the intervention and facilitates implementation [195].

The *implementation phase* (Phase 4) refers to moving the intervention into a real-world setting and evaluating implementation processes, such as the uptake and sustainability of the intervention [195, 196]. The implementation phase can be viewed as a separate phase with its own frameworks to evaluate and improve the implementation of the intervention [195, 196, 199, 200].

1.4.1.1 Assessing feasibility of interventions

In contrast to traditional research studies examining effect outcomes, pilot and feasibility studies can be defined as *pre-study research*, with research questions concerning aspects of the study processes, methods, or design [198]. A pilot study is often conducted as a small-scale replica of the main trial, whereas a feasibility study is not necessarily conducted with the same study design or protocol, or even to assess the same outcomes as those planned for the main trial. A feasibility study is applied to collect pieces of information required to formulate the plan for the main study, with the main aim of informing the development and conduct of a planned research project. As such, the research questions to assess feasibility will dictate the design. Which feasibility aspects should be assessed is not *standardized*, but largely depend on the specific uncertainties related to the intervention of interest. Examples of aspects that can be assessed in feasibility studies include [198]:

- procedures related to the time and resources required for delivery of the intervention;
- methodological performance of new devices/technical solutions (e.g., eHealth solutions);
- clinical aspects related to introducing an intervention into a setting;
- participant and other stakeholders' acceptability of the intervention.

If it is considered that multiple procedural, methodological, and clinical aspects need to be tested, conducting the whole intervention can provide the information needed to assess important feasibility and acceptability aspects [198]. Evaluation of the feasibility outcomes should be conducted according to predefined criteria or thresholds, but the feasibility goals should be balanced between what is ideal and what is realistic in a real-world setting [195, 198].

1.5 Sustainable delivery of management programs

1.5.1 Web-based delivery

The area of eHealth is defined as "*the use of information and communication technologies for health*" [201] and includes a variety of technologies to deliver healthcare or self-management support, such as web-based information and interaction, mobile technologies and real-time monitoring devices [202]. The use of eHealth and digital solutions is recognized as a potential approach to enable more accessible, sustainable care and support for large groups of patients with musculoskeletal conditions [202].

A Cochrane review of 24 RCTs reporting on the effects of interactive health communication applications for people with various chronic diseases found that users of interactive applications tended to gain more knowledge, felt they had better social support, and had improved health behavior and health outcomes than non-users, but the authors stated that there was a need for more high-quality studies to confirm their preliminary findings [203]. Another systematic review of seven RCTs compared the efficacy of eHealth-supported home exercise to controls with regard to pain, physical function, and health-related quality of life in patients with knee OA [204]. Overall, eHealth-supported home exercise gave small short- and long-term improvements in pain, physical function, and health-related quality of life [204].

A few established programs offer digitally delivered self-management support for people with OA, and two of these have demonstrated that digital solutions may have the potential to support exercise adherence and beneficial outcomes [205-208]. The Dutch Join2move program offers a fully automated web-based program comprising nine weekly modules with education and behavioral graded activity to improve physical activity and decrease pain [207, 208]. Results from a study in which 199 people were randomized to the Join2move program or a waiting list control group showed that many participants completed the first two modules, but few utilized all nine modules [208]. At 3 months follow-up, physical function was significantly improved in the intervention group compared to the control group, without any difference between the groups at 12 months. Neither of the groups had an increased physical activity level [208]. Another program, the Joint Academy program, is a web-based OA treatment platform based on the Swedish BOA program [205, 206]. An observational study of 350 people participating in a 6-week Joint Academy program showed that participation was associated with beneficial outcomes for pain, physical function, and health-related quality of life among the 250 participants reporting at follow-up [206].

In all, digital delivery of self-management support is in its infancy. Digital, web-based delivery of management programs to support exercise adherence and long-term beneficial health outcomes may potentially be part of the solution to future healthcare challenges. Therefore, examining the feasibility, effects, and sustainability of innovative methods of delivering management programs should be put on the research agenda.

1.5.2 User involvement and peer-support

User involvement is required by law within the Norwegian healthcare service. User involvement is a tool for developing high quality healthcare services and a way to ensure quality of care and increase the accuracy of the offered services. The voices of patients and their relatives should be heard, and patients have the right to make their own choices regarding their health. Traditionally, patients have been passive recipients of health services, but now they have the right to and are expected to participate in a collaboration with healthcare professionals, aiming at shared decision-making.

Along with the recognition of user involvement in healthcare, user involvement in research has also emerged. Patients collaborating in research are called patient research partners. Patient research partners have specific experience competency, such as living with a specific disease [209]. The concept of patient involvement is rooted in the well-known idiom, "Only the wearer knows where the shoe pinches." The patient research partners' specific competency is regarded as being equal to other forms of relevant competency in a research group and, altogether, the different competencies are supposed to strengthen the study and the validity of the results. In 2011, the EULAR made strong recommendations for user involvement in all research projects, which included collaboration between researchers and patient partners in all phases of a project to facilitate relevance, quality, and validity of the research process [209]. Currently, the EULAR's patient representative organization (People with Arthritis/Rheumatism across Europe, PARE) consists of individuals from national patient organizations, representing more than 30 European countries, including the Norwegian Rheumatism Association, that are "speaking the patients' voices" by being involved in research for rheumatic and musculoskeletal diseases [210].

Patient organizations and their representatives can also provide more direct support [209]. A Cochrane review of five RCTs reported that user involvement in designing patient information resulted in more patient-friendly material, which could improve patients' knowledge, indicating the importance of the patient perspective on educational components of

self-management strategies [211]. Making self-management information understandable in line with the patients' level of health literacy is a prerequisite for information uptake [212]. In terms of web-based patient information, eHealth literacy is defined as "*the ability to seek, find, understand, and appraise health information from electronic sources and apply the knowledge gained to addressing or solving a health problem*" [213], underlining the importance of accessible and understandable patient information on trustworthy websites. Importantly, uptake of the information makes patients well-informed, which in turn can facilitate adoption of and adherence to effective self-management strategies.

In chronic diseases, strategies for self-management support include not only patient information, but also strategies to support problem-solving and self-efficacy in real-life situations [214], such as support to maintain exercise as part of life-long treatment. Coulter and Ellins summarized substantial evidence to examine the effectiveness of strategies to inform, educate, and involve patients in their treatment of chronic diseases [212]. Out of 67 systematic reviews examining self-care and self-management strategies, a positive effect on *patients' knowledge* was found in all of the 19 reviews reporting on this outcome. The effect on *health behavior and health status* were reported in 50 of the reviews, including 39 reporting a beneficial effect, 15 reporting mixed effects, and 6 reporting negative effects [212]. Although the authors stated a large knowledge gap regarding the long-term outcomes of self-management interventions, the substantial evidence base underlines the power of patient education and self-management support in promoting uptake of knowledge, adherence to positive health behavior, and beneficial health outcomes. Thus, providing long-term support has the potential to reinforce the positive effects of self-management interventions and produce beneficial long-term outcomes for the many people with chronic diseases, such as OA.

Support for self-management has largely focused on healthcare practitioners' knowledge and competence to provide patient-centered care [119, 215]. A challenge is that the interaction between healthcare practitioners and patients is limited by lack of time and resources, and that the patient's self-management behavior most often plays out in real-life, everyday settings. It is well known that, after close management support in rehabilitation programs, patients with chronic diseases are often unprepared for the challenges of self-managing in daily life, suggesting that timely and sustained support outside of the healthcare setting can facilitate improved self-management [216]. Peer-support has been shown to be effective in promoting health behavior in chronic diseases, such as diabetes [217]. Fisher and colleagues identified 65 studies (including 24 reviews) to examine the impact of peer-support on the management of

complex, sustained health behavior. In all, 54 studies reported a significant impact of peer-support, and the authors concluded that, across diverse settings and healthcare systems, peer-support is effective in promoting self-management of complex health behavior. Some studies did not find beneficial effect of peer-support due to interventions not fitting the patients' needs or possible harm of unmoderated peer-support [217], suggesting that peer-support should be provided by "qualified" individuals.

Many patient organizations have an established network of qualified peer-supporters who are educated and trained by the organization. For example, the Norwegian Rheumatism Association has a network of 500 peer-supporters across 215 local teams all over Norway [218]. Based on education, training, and specific experience and competence related to living with a chronic disease, they may be a valuable resource in providing guidance and support to peers. Such solid and qualified networks of peers could probably be utilized as an extension of the healthcare system under pressure, such as by providing support for patients in need of long-term follow-up of exercise as part of treatment.

1.6 The importance of adherence

The World Health Organization has defined adherence as, "*the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a healthcare provider,*" and put forward adherence to treatment as the single most important modifiable factor that should be optimized to achieve desired outcomes [219]. Adherence to treatment is addressed to a varying degree in OA guidelines and recommendations [117, 118, 125, 126, 133]. The OARSI guidelines state that re-assessment after initiating treatment gives the opportunity to explore barriers to adherence and adjust treatment dosage [125]. The EULAR recommendations for physical activity in individuals with inflammatory arthritis and OA state that physical activity interventions should always incorporate behavioral change techniques to promote long-term adherence [133].

The field of exercise adherence in OA has gained increasing attention in the last few years, and adhering to exercise is currently recognized to be based on complex health behaviors [189, 220]. Non-adherence has been reported to be one of the most important barriers to achieving and maintaining the beneficial effects of OA treatment [221].

For many people with OA, adherence to exercise recommendations may require significant changes in everyday behavior, and a complex interplay between barriers and facilitators may influence a person's adherence to activity and exercise [189]. Based on 12 qualitative studies, Hurley and colleagues synthesized factors within four themes that influence people with OA to participate in exercise and physical activity (**Figure 8**) [189].

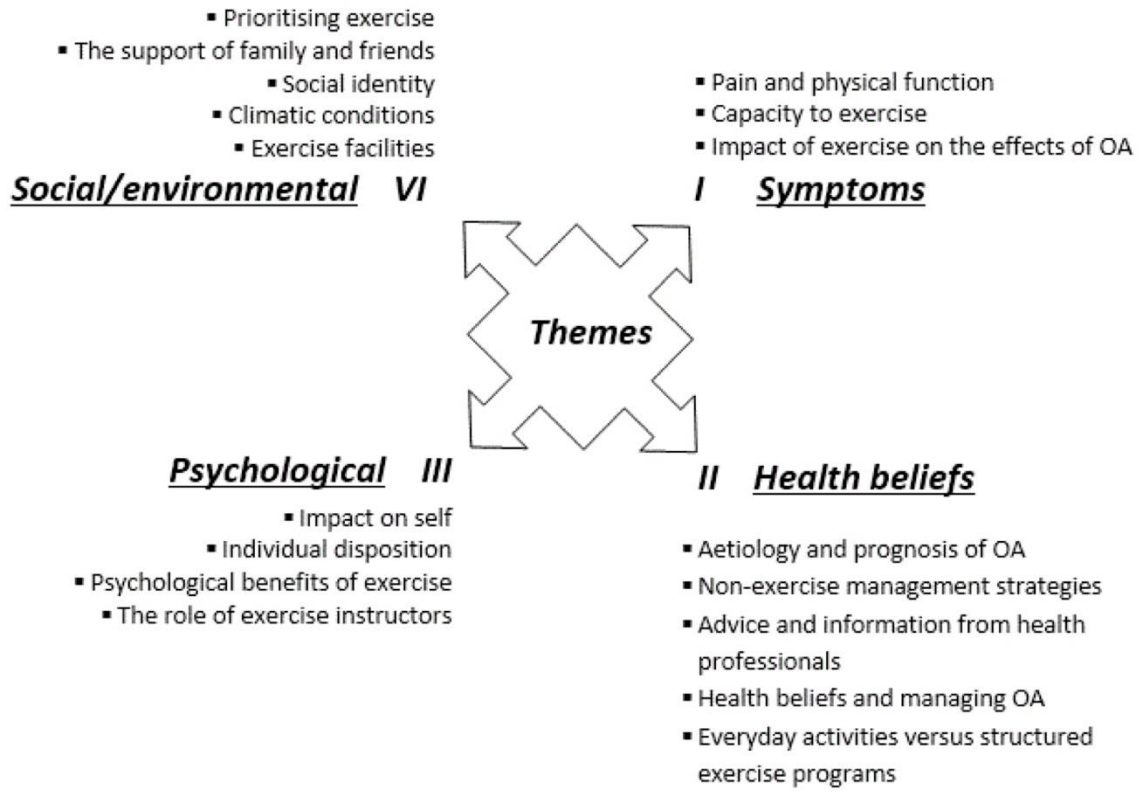

Figure 8. Factors influencing participation in exercise and physical activity [189] (Printed with permission from John Wiley and Sons).

Patients perceived physical capacity, severity of symptoms, and pain and fatigue following exercise can make some patients feel less able to exercise regularly, but the hope that exercise reduces pain can also be a motivating factor for exercising [189]. Factors such as motivation, perceived pain, and social support may be both barriers and facilitators, and the interplay between them may change over time [222]. A negative pain experience during or after exercise can result in decreased motivation for continued exercise, whereas experiencing pain relief after exercise can increase motivation for continued exercise [223]. Given the multidirectional array of factors that may affect the decision to exercise [222], emphasis has been put on identifying modifiable factors to provide individualized management strategies that promote adherence [220].

Modifiable barriers and facilitators that can influence exercise adherence among individuals with hip and/or knee OA were identified in a literature review of 15 quantitative, 6 qualitative, and 2 mixed-methods studies [224]. The studies involved various interventions, i.e., different types of supervised, unsupervised, and self-initiated exercise, and different modes of delivery. Barriers and facilitators were categorized according to the Theoretical Domains Framework, which applies several behavior-change theories to explain changes in behavior according to distinct domains (e.g., "environmental context and resources", "knowledge", "skills", "beliefs about capabilities", "beliefs about consequences", "social influences", and "reinforcement" [178, 179, 224]. The review showed that many barriers and facilitators could be categorized into the "environmental context and resources" domain [224]. Access to facilities, cost of exercise, safety concerns, transportation, and parking were considered barriers, whereas easy access to suitable group sessions and low-cost group sessions were facilitators to exercise adherence. Other identified barriers were related to "beliefs about consequences" (i.e., beliefs about the consequences of exercise), whereas "reinforcement" facilitators included pain relief and encouragement from health practitioners. In the "social influences" domain, facilitators for exercise adherence included social support from family, training partner, or peers [224].

Supervised exercise is known to improve outcomes for patients with OA in terms of reduced joint pain, improved physical function, and better health-related quality of life [141-143, 147, 225, 226]. However, these studies underline that the beneficial effects are dependent on the patient's adherence to the exercise program and will attenuate with decreased adherence.

A Delphi survey resulting in 10 core evidence-based guidelines to guide healthcare practitioners in delivery of exercise for OA advocated adherence to exercise as the principal predictor of long-term outcomes in patients with hip or knee OA [227]. This core guideline was supported by five RCTs [227]. In one of the RCTs, 786 adults with knee OA were given an exercise plan focusing on maintenance and improvement of muscle strength, and they were encouraged to exercise 20-30 minutes per day [228]. Adherence was recorded by diaries collected every 6 months. After 2 years, the authors graded adherence as low (n=307), medium (n=32), or high (n=128) and found that the effect on pain relief was better with adherence to a greater number of exercise sessions [228].

A systematic umbrella review including six meta-analyses and three systematic reviews examined the effects of physical activity and exercise on pain, physical function, and health-

related quality of life among individuals with lower limb OA [226]. The evidence supporting more beneficial outcomes for pain and physical function in those with a higher level of physical activity and exercise relative to less active people was strong, and the evidence supporting more beneficial outcomes for health-related quality of life was moderate. The authors reported that even as little as 45 minutes, and up to 150 minutes, of moderate intensity activity per week is associated with sustained high or improved function, and that the benefits of physical activity and exercise persisted up to 6 months following cessation of a structured program [226]. One of the meta-analyses included in the umbrella review reported that adherence in terms of participating in a greater number of supervised aerobic sessions significantly increased improvement in pain and non-significantly improved physical function [142]. Similar beneficial effects of participating in more exercise sessions was not found for strengthening exercise [142]. Another meta-analysis included in the umbrella review examined the effect estimates for pain and function immediately after the exercise program between patients participating in <12 versus ≥12 "face-to-face" supervised exercise sessions and reported no significant differences between the groups [143]. Another robust study of OA patients reported that only 39% of the patients completed at least two supervised strengthening sessions per week at the recommended intensity [229]. Importantly, only exercise sessions performed with the recommended intensity were counted as "adhered" in this study, displaying the challenges related to measuring and reporting adherence [229].

The challenges related to reporting and measuring adherence were underlined in a Cochrane review of 42 RCTs that examined the effects of interventions to improve adherence to exercise and physical activity in individuals with chronic musculoskeletal pain [230]. The authors warranted a need for high-quality RCTs with long-term follow-up that specifically address adherence to exercise and physical activity, and that a standard validated measure of exercise adherence should be used in future studies addressing adherence [230]. Two more recent systematic reviews evaluated tools to measure adherence to musculoskeletal treatment, concluding that accurate high-quality tools for measuring adherence are lacking [231, 232].

Even if exercise is shown to effectively improve symptoms in individuals with OA, long-term adherence seems to be a challenge for many patients with chronic musculoskeletal diseases. A systematic review and meta-analysis of 11 RCTs assessed the effectiveness of OA interventions in promoting long-term physical activity behavior [233]. Self-management programs were reported to contribute to small, short-term increases in physical activity, but

the effect declined with no remarkable difference compared to controls beyond 12 months of follow-up [233].

Physical activity is important for all people, and exercise is recommended as part of the treatment plan for large groups of patients. There is a well-known dose-response relationship for exercise, as there is for medication, and the detailed description of dosage within the concept "Exercise Is Medicine" is decisive.

A Cochrane review aimed to examine the outcomes of high intensity versus low intensity exercise programs in individuals with hip or knee OA [145]. Based on the six identified studies, the authors concluded that there was insufficient evidence to determine the effect of different types of intensity of exercise programs [145]. Another meta-analysis of 12 RCTs focusing on high and low or uncertain compliance with the ACSM exercise dose recommendations showed that supervised exercise with high compliance to the ACSM dose recommendations results in significantly larger improvements in pain than interventions with uncertain compliance [147, 225]. For self-reported physical function, non-significant improvements were reported, but the authors reported that few of the included studies sufficiently assessed outcomes to evaluate the objective physiological outcomes of exercise [147, 225].

Social support and environmental factors are reported to be important for participation in physical activity [234]. The importance of social support was underlined in a review of 30 RCTs including patients with various musculoskeletal diseases [235]. This review pointed at self-efficacy and previous adherence to exercise as factors that increase adherence [235]. Furthermore, the positive effect of booster sessions was highlighted in two systematic reviews [236, 237]. A meta-analysis of nine studies including older adults with chronic low back pain and hip or knee OA reported positive effects of booster sessions in improving adherence to exercise after the formal program ended [236]. Pister et al. concluded that the beneficial effect on symptoms immediately after treatment was not sustained in the long-term, but providing a booster session after the treatment period improved the long-term outcomes [237]. The knowledge about booster sessions is worth noting. They have the potential of being effective in the management of patients with OA and may be feasible and fit well into the logistics of everyday clinical practice.

In summary, improved clinical routines are obviously needed to gain more insight into the many aspects of adherence to recommended exercise. Standardized use of valid methods for measuring adherence and more detailed descriptions of exercise doses are factors that could

potentially contribute to moving the field forward and provide more optimal healthcare for patients with OA.

1.7 Rationale for this thesis

OA is a chronic disease that presents with varying severity, but the disease burden in terms of pain and functional limitations is substantial for many patients. An aim of this project was to enlighten how functional limitations present in age-groups of OA patients.

It is well known that exercise is medicine for patients with chronic diseases, such as OA, but exercise referred as part of a treatment program requires individual adaptation of the program, adjustment of the dosage over time, and tight follow-up to ensure long-term adherence. For this purpose, individually tailored exercise programs and feasible tools for measuring patients' habitual physical activity are needed. Therefore, we aimed to examine the validity of patient-reported activity compared to objectively measured physical activity.

The long-term needs of the large group of OA patients for support and follow-up cannot be met solely by healthcare professionals, and alternative methods for delivery and follow-up of health-related exercise programs are urgently needed. Patient organizations, with their established networks of educated peer-supporters may be an unutilized resource. The peer-support model is based on the belief that patients have a unique competence in supporting and motivating other patients and may serve as a powerful and continued source of support for patients in need of long-term adherence to exercise, possibly playing a role as an extension of the health care service. To test this hypothesis, an aim of this project was to examine the feasibility of and patient adherence to a web-based, peer-supported exercise program for patients with OA that was developed and carried out in collaboration between specialized healthcare services and a patient organization.

2 Aims and research questions

The overall aim of the thesis was to contribute to development of feasible and sustainable management of patients with OA. The project is based on three research purposes: 1) to explore physical function (in terms of walking ability) in OA patients, 2) to assess the validity of tools for measuring habitual physical activity, and 3) to examine the feasibility of and adherence to a web-based, peer-supported exercise program as part of treatment for OA patients.

The specific research objectives were:

- To compare functional capacity (walking ability) in age- and gender-matched groups of patients with OA and the general population (Paper I).

- To assess the validity of a physical activity questionnaire (IPAQ-SF) by concurrent use of an accelerometer as a criterion measure in patients with OA (Paper II).

- To explore the feasibility of a 12-week web-based, peer-supported exercise program delivered by a patient organization to patients with hip and/or knee OA (Paper III).

- To explore the adherence to a 12-week, web-based, peer-supported exercise program in patients with hip and/or knee OA and map barriers for completing the exercise sessions (Paper IV).

3 Materials and methods

3.1 Study designs

Various study designs have been used to answer the research questions in this thesis. A cross-sectional, comparative design was used to explore physical function in an OA population compared to a reference sample from the general population, whereas associations between physical function and risk of CVD comorbidity were examined only in the OA cohort (Paper I). For methodological purposes, a cross-sectional design was used to examine the criterion validity of a self-reported physical activity questionnaire compared to physical activity objectively measured with an accelerometer (Paper II). An experimental, single-arm, pre-post design was used to examine the feasibility of and adherence to a web-based, peer-supported exercise program for patients with hip and/or knee OA (Papers III and IV).

3.2 Development of the AktiWeb program

The web-based, peer-supported AktiWeb program was developed in line with the MRC framework for developing and evaluating complex interventions [190, 195].

The AktiWeb program was developed as a collaboration between researchers at Diakonhjemmet Hospital and the Norwegian Rheumatism Association. The project group developing the program comprised the PhD candidate of the project (Kenth Louis Joseph), a healthy life consultant in NRF (Ole-Martin Wold), a patient research partner in NRF (Knut Øderud), supervisors of the project (Anne Therese Tveter, Hanne Dagfinrud, and Kåre Birger Hagen), and members of the research group (Anne Christie, Kristine R. Nordén, Camilla Fongen, Rana S. Hinman, Rachel Nelligan and Kim L. Bennell).

The program contained a website with OA information, an exercise program, a digital exercise diary, motivational messages, and peer-support. An overview of the main components of the program is shown in **Figure 9.** The design of the program was based on experiences from an exercise and healthy lifestyle program (named *Kom i Form*) developed by the patient organization Norwegian Rheumatism Association.

The *Kom i Form* exercise and healthy lifestyle program was developed to support individuals with musculoskeletal disease in improving their quality of life and was launched by the

patient organization in January 2018 [238]. The 8-month program was delivered by SMS with a URL to web-based patient education and exercise material and comprised monthly themes, such as motivation for a healthy lifestyle, strength and aerobic exercise, nutrition and physical activity. Participants also received weekly videos of exercises and access to a closed Facebook group for motivation and inspiration [238].

As part of the development of the AktiWeb program, an anonymous evaluation survey was published on the *Kom i Form* Facebook group asking about experiences attending the program and open-ended questions about how the program could be improved. The survey was answered by 133 individuals, most of whom were women >50 years of age. In general, the feedback was positive, but some participants considered the web-based instructions and information to be too extensive. Thus, in developing the AktiWeb program, we aimed to make the instructions and information as concise as possible.

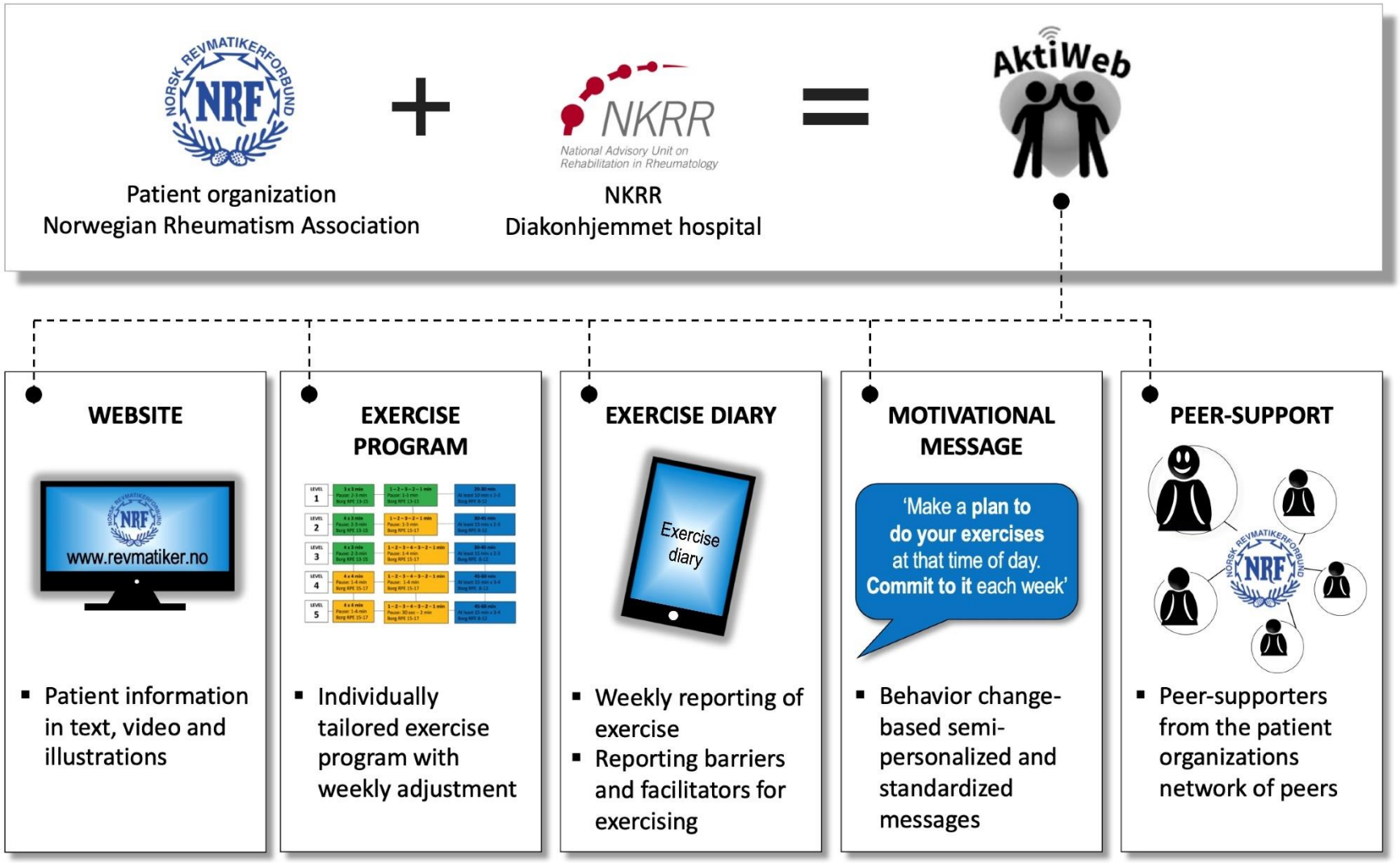

Figure 9. Overview of the main components in the AktiWeb program

3.2.1 The website

The AktiWeb website was incorporated into the patient organizations official website. The website comprised educational patient information about:

- *OA treatment*
  First-line core treatment, adjunctive treatment, and surgery for hip or knee OA, including a video of a health professional informing viewers about recommended treatment options [117, 119, 239].
- *OA symptoms*
  Exercise and activity-related OA symptoms (pain and swelling) that could be expected, and symtoms indicating that the exercise should be adjusted, including illustration of an NRS-based scale ranging from 0 (no pain) to 10 (worst imaginable pain) to guide evaluation of pain experience related to exercise and activity.
- *Exercise – why it is beneficial for OA*
  Plain language summary of the evidence-based beneficial effects for pain, physical function and health-related quality of life. Possible symptom-modifying mechanisms (neuromuscular, intra-articular and peri articular components).
- *Exercise and general physical activity*
  General health benefits of exercise (strengthening and aerobic) and physical activity, including the physical activity guidelines. *What* exercise is, *why* do it, and *how* to do it.
- *The BORG Rating of Perceived Exertion (RPE) scale*
  How to use the BORG RPE scale to control intensity of exercises, including the possibility to read additional explanation of the different BORG scale ranges.
- *The AktiWeb exercise program*
  The five different exercise levels, including the possibility to download description of each exercise session and the complete exercise program.

3.2.2 The exercise program

3.2.2.1 Development of the program

The exercise program was developed based on the most recent guidelines and recommendations for exercise in individuals with hip and/or knee OA [117, 126, 133, 240]. The 2011 ACSM recommendations for exercise for healthy adults was endorsed by a EULAR task force in 2018, advocating that a target aerobic exercise dose of at least 500-1000 Metabolic equivalent of task (MET)-minutes per week is safe, has health benefits for hip/knee OA, and is generally an important part of optimizing health-related quality of life [133, 241]. The task force stated that lower exercise dosages may be beneficial for those who are unable or unwilling to reach the minimum recommended exercise dose [133]. In line with this, the program was designed to focus on aerobic exercise with the intent to improve aerobic capacity and comprised five different levels, with each level consisting of three aerobic exercise sessions per week. The "lowest" exercise level (level 1) started at 175-230 MET-minutes per week, progressing to the "highest" level (level 5) with 445-535 MET-minutes per week. Initially, the exercise levels were set somewhat higher (from 260-310 at the lowest level to 585-660 at the highest), but the patient research partner's experiences and involvement led to adjustments to the weekly exercise dose. A detailed description of the content of the final exercise levels is given in **Figure 10**. The intensity of each session was described using the BORG RPE scale, ranging from 6 (resting) to 20 (maximal exertion) [242]. Each exercise session was described concisely in text and by an illustration including practical suggestions on how to perform the sessions indoors or outdoors.

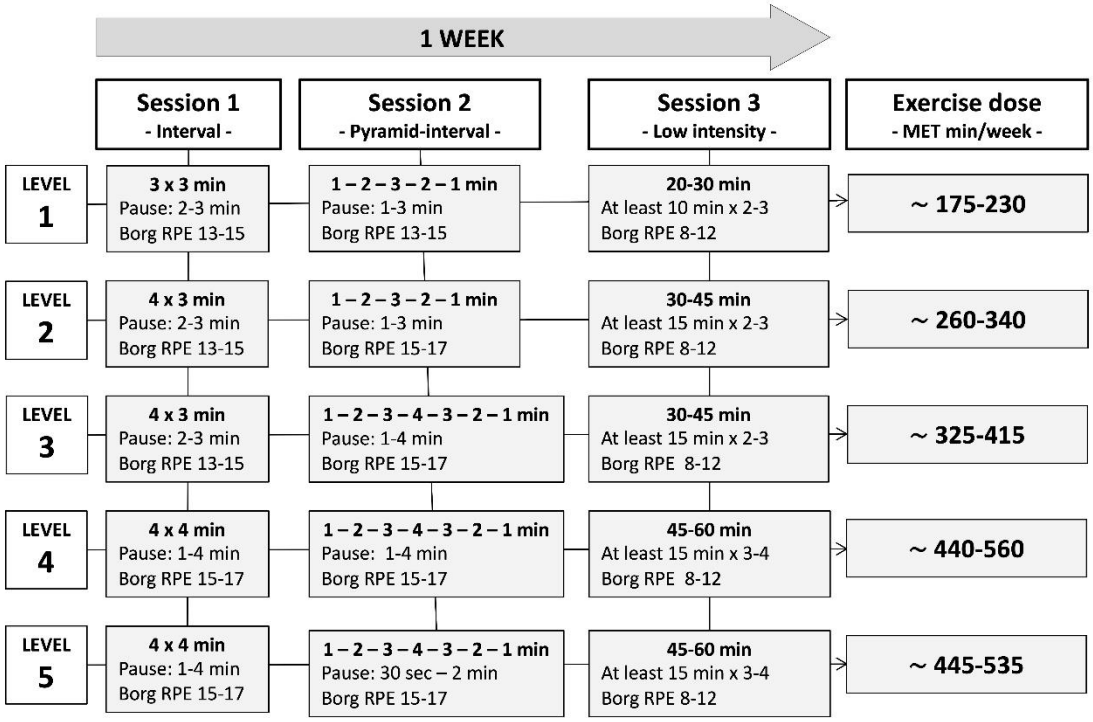

Figure 10. Description of the sessions in the five exercise levels including frequency (number of intervals), duration (time of intervals), intensity (BORG RPE), and total MET-minutes per week, and the minimum and maximum duration of active pauses between the intervals. Active pause = 3.3 MET, BORG RPE 8-12 = 3.3 MET, BORG RPE 13-15 = 4.0 MET and BORG RPE 15-17 = 8.0 MET [243].

3.2.2.2 Individually tailored exercise dosages

The initial tailoring of exercise dosages was based on baseline screening in which the exercise level the first week was determined by predefined criteria (**Table 2**). For example, the primary criteria were completion of the maximal cardiorespiratory test. If the test was not completed, the lowest exercise level (level 1) was assigned. Tailoring of the exercise dose in subsequent weeks was based on the digital exercise diary.

Table 2. Criteria for determining a patient's exercise level the first week

Exercise level	Clinical evaluation in addition to:
1	Not completing maximal exercise test *or* VO_{2peak} <reference values *and* PA habits <1-2 per week
2	VO_{2peak} <reference values *and* PA habits ≥1-2 per week *or* VO_{2peak} ≥reference values *and* PA habits 1-2 per week *and* NRS pain in activity ≥6
3	VO_{2peak} ≥reference values *and* PA habits 1-2/week *and* NRS pain in activity <6 *or* VO_{2peak} ≥reference values *and* PA habits ≥3/week *and* NRS pain in activity ≥6 *or* VO_{2peak} <10% above reference values *and* PA habits ≥3 per week *and* NRS pain in activity <6
4	VO_{2peak} ≥10% above reference values *and* PA habits ≥3 per week *and* NRS pain in activity <6 *and* performing interval exercise <1-2 per week
5	VO_{2peak} ≥10% above reference values *and* PA habits ≥3 per/week *and* NRS pain in activity <6 *and* performing interval exercise ≥1-2 per week

VO_{2peak} = peak oxygen uptake, PA = physical activity, PA habits = PA of at least 30 min with increased respiration and heart rate, performing interval exercise = performing regular interval exercise the last 3 months, NRS = numeric rating scale (10=worst pain). VO_{2peak} reference values (specific for gender and age group) were retrieved from Edvardsen et al. [244].

3.2.3 The exercise diary

The digital exercise diary was developed to collect information about adherence to the exercise program, asking which of the three weekly sessions were completed according to the prescribed BORG RPE intensity. After the first week, the exercise levels for the following weeks were based on reporting in the exercise diary. The exercise level was increased (until reaching level 5) if the patient reported having completed the exercise program the past week. If the program was not completed, the program was kept at the same level. In addition, those reporting not having completed all of the weekly sessions were asked for the reasons (described as barriers below).

3.2.4 Motivational messages

The motivational messages used in this program were based on the messages described by an Australian research group [245]. The messages were developed to support adherence to self-directed, progressive strengthening exercise for individuals with knee OA. The message library was developed based on the Behavior Change Wheel Framework, which is a synthesis of 19 behavior change models [180, 245]. The library comprised messages designed to overcome a set of selected barriers (forgot, too tired, joint hurts so I cannot exercise, worried exercise is causing pain/injury, exercise is not helping, boring, lack of time, life stress, none of the alternatives apply to me) and general messages to facilitate exercise adherence [245].

To implement the messages in the AktiWeb program, they were conveniently translated from English to Norwegian to make them suitable for delivery by email to patients with both hip and knee OA and relevant for aerobic exercise. A library of different messages to overcome the predefined barriers, as well as different messages to facilitate adherence, allowing for the provision of unique weekly messages intended to promote exercise adherence. In addition, individual messages were formulated for patients reporting barriers other than those that were predefined.

3.2.5 Peer-support

In the AktiWeb project, two experienced peer-supporters from patient organization volunteered to offer support by phone to the participants in the study. Peer-support was included because such support may be important for self-management, including uptake and adherence to regular exercise [189, 217, 224]. The names and mobile phone numbers of the peer-supporters were shared with the study participants by email together with the exercise program.

3.3 Study samples

This thesis is based on three different study samples comprising individuals with OA, as well as a reference sample. In total, data on 858 individuals were included in the analyses of the different papers. An overview of the number of participants included in the analyses in each paper is provided in **Table 3.**

Table 3. Overview of the participants with OA included, and the inclusion and exclusion criteria, in Papers I, II, III, and IV.

	Paper I		**Paper II**	**Papers III and IV**
	OA sample	***Reference sample***		
n	500 (362 women, 138 men)	235 (121 women, 114 men)	93 (81 women, 12 men)	30 (21 women, 9 men)
OA sample	- Subsample of inhabitants in Ullensaker municipality aged 40-80 years who self-reported OA	*Not applicable*	- Patients referred to a specialized healthcare OA patient education course requiring a doctor-confirmed OA diagnosis (hip, knee, hand)	- Patients referred to surgical consultation at specialized healthcare due to radiographic OA (hip and/or knee)
Inclusion criteria	- Self-reported OA by the question: "Have you ever been diagnosed with OA in hip/knee/hand by a medical doctor and/or x-ray?" - Participated in the medical examinations and/or physical tests	- Age 40-80 years	- Age ≥18 years - Independent of walking aids - Competent in Norwegian	- Age 40-80 years - OA in the hip and/or knee - Not candidate for surgery
Exclusion criteria	- Self-reported inflammatory rheumatic disease and/or history of cardiovascular disease	- Unable to walk - Not understanding Norwegian	- Unable to walk - Not understanding Norwegian	- Not understanding Norwegian (verbal and written) - Unable to walk about/ambulatory walk continuously for 15 minutes - Relatives with sudden death before 40 years of age - First-degree relatives with heart disease - Absolute or relative contraindications for maximal exercise testing

3.4 Study recruitment

Paper I comprised a study sample of participants with OA and a reference sample. The OA sample was based on the observational, population-based Musculoskeletal pain in Ullensaker STudy (MUST) that was initiated in 2010 to gain more knowledge about musculoskeletal pain and the risk factors, management, and consequences of OA [246]. Participants in the MUST study were recruited by postal invitation, which was sent to all inhabitants aged 40-80 years in Ullensaker municipality. The invitation included a questionnaire, and people who consented to participate and further self-reported OA (hip, knee, hands) in the questionnaire were defined as a population-based subsample with OA. This subsample was further invited to answer questionnaires addressing OA and CVD factors and participate in a comprehensive examination at Diakonhjemmet Hospital [246]. Individuals in the reference sample were recruited in a separate study that aimed to provide reference values for health-related physical fitness measures in patients with musculoskeletal disorders [247]. Data from a total of 500 participants from the OA sample and 235 individuals from the reference sample were included in the different analyses in Paper I (**Figure 11**).

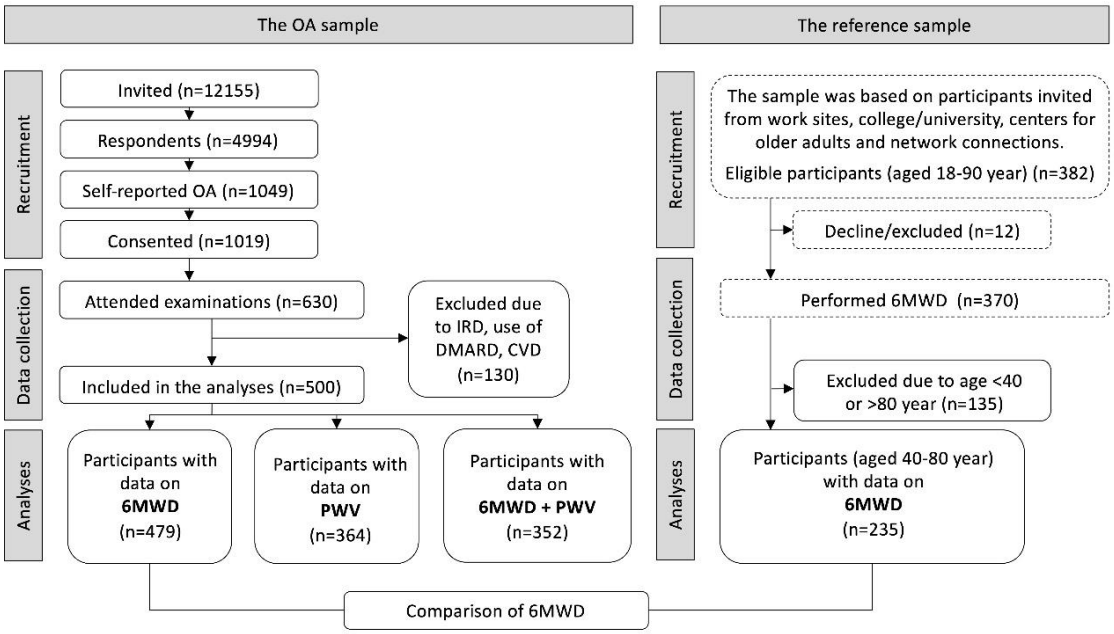

Figure 11. Flowchart of participants included in the study samples in Paper I. IRD, inflammatory rheumatic disease; DMARD, disease-modifying antirheumatic drug; CVD, cardiovascular disease; 6MWD, 6-minute walking distance. Boxes in stapled lines represent recruitment processes conducted in the separate study [247].

In Paper II, patients were recruited from OA patient education courses held two or three times per month at Diakonhjemmet Hospital. The recruitment period lasted from November 2017 to June 2018. Posters and flyers with brief information about the study were placed in the waiting area for patients to read. In addition, during the course, the course administrator briefly informed all patients about the study and how to contact the project associate on site during the break or after the course if they were interested in participating. All participants received oral and written information about the study before giving their written consent. The total number of patients attending the courses was collected from attendee lists recorded by the course administrator. Among the 115 consenting participants, those with missing data or insufficient physical activity data were excluded, leaving a total of 93 participants in the analyses (**Figure 12**).

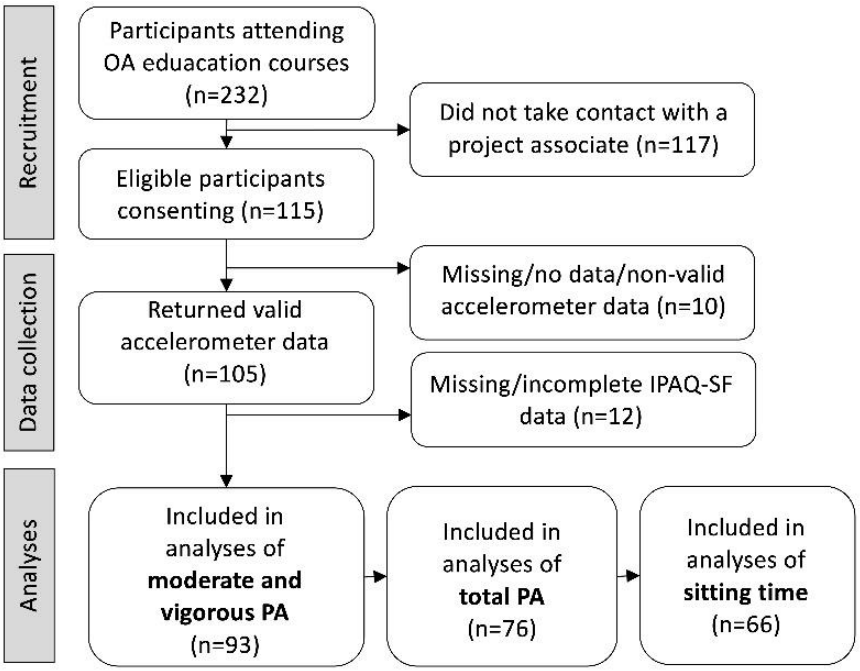

Figure 12. Flowchart of participants included in the study sample in Paper II. PA = physical activity

In **Papers III and IV**, the participants were invited into the study after consultation with an orthopedic surgeon at Diakonhjemmet Hospital due to radiographic hip and/or knee OA.

Patients who were not candidates for surgery were pre-screened by the surgeon conducting the consultation, and 49 patients were identified as eligible and given written and verbal information about the study by a project associate. Patients who agreed to participate in the study were screened for the inclusion and exclusion criteria (**Table 3**) before collecting their signed consent form. For those who declined to participate, reason for declining were recorded. In Paper III all patients were part of the feasibility study sample, and in Paper IV patients participating in baseline assessments were included in the study sample (**Figure 13**).

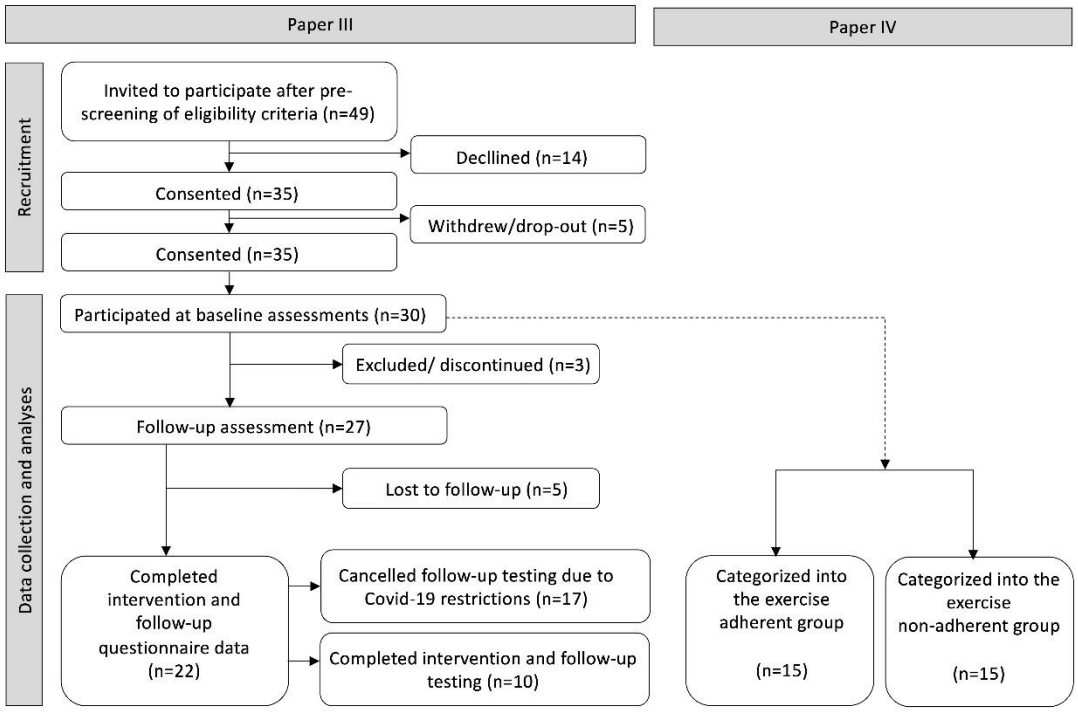

Figure 13. Flowchart of participants included in the study sample in Papers III and Paper IV.

3.5 Data collection and procedures

Data were collected using paper-based or digital questionnaires and through medical examinations, physical testing, and assessment of physical activity. An overview of timelines for the data collection are illustrated in **Figure 14**.

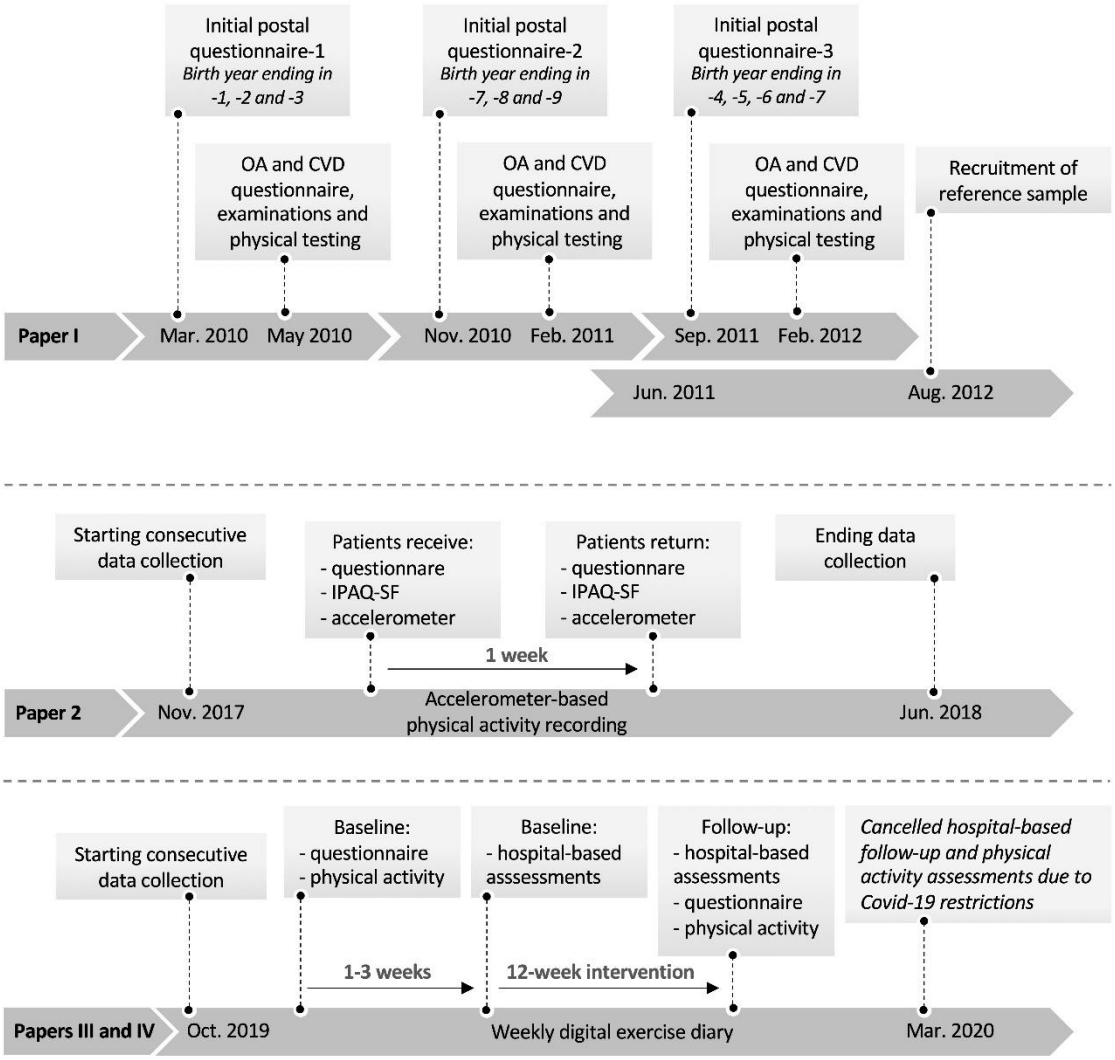

Figure 14. Overview of timelines for the data collection in Papers I-IV.

In Paper I, a comprehensive amount of data was collected on participants with OA using postal questionnaires and through examinations and physical testing at Diakonhjemmet Hospital [246]. We used data collected by the initial postal questionnaire and the second OA- and CVD-specific questionnaires, as well as data from radiographs, blood samples, clinical findings, physical tests, and pulse wave velocity measures. Data that were based on

radiographs, blood samples, and clinical findings were used to define individuals with OA (hip, knee, hand) according to the ACR classification criteria [21-23].

In Paper II, we collected data by paper-based questionnaires, accelerometers, and diaries on usage (dates and hours) of the accelerometer. The data collection material was provided to participants on site at the OA course by a project associate. The participants were instructed to wear the accelerometer for 7 consecutive days counting from the next morning. Participants who wanted to start using the accelerometer at a later timepoint (i.e., due to traveling), received the study material by post at a scheduled date. To ensure concurrent measures of physical activity, which was measured prospectively by the accelerometer and retrospectively (last 7 days) through the physical activity questionnaire, all participants received a text message as a reminder to answer the physical activity questionnaires after wearing the accelerometer for 7 days. The questionnaire and accelerometer were returned by post using a prepaid envelope. If the study material was not returned within 1-2 weeks after the assessment period, the participants received a reminder (SMS or phone call) from a project associate.

In Papers III and IV, we collected baseline and 12-week follow-up data using accelerometers, digital questionnaires, and cardiorespiratory treadmill tests. During the intervention, data on weekly exercise compliance were obtained by a digital exercise diary. Both the questionnaire and the exercise diary were collected through Nettskjema (www.nettskjema.no), which sends encrypted data to the Service for Sensitive Data (TSD), a secure system for storing sensitive data in accordance with the Personal Data Act and Health Research Act in Norway (owned by the University of Oslo, USIT).

After giving written consent to participate in the study, the patients were scheduled for an appointment at Diakonhjemmet Hospital within 1-3 weeks. Prior to this appointment, the patients were instructed to wear the accelerometer for 7 consecutive days and to answer the digital questionnaire. The accelerometer was returned at the scheduled appointment. A physiotherapist experienced in treadmill testing conducted the VO_2 testing and screened the participants with regard to determining the initial exercise level. After completing the baseline assessments, the participants initiated the 12-week intervention. A follow-up treadmill test was scheduled after completion of the 12-week intervention. Prior to the follow-up treadmill test, the participants answered an electronic questionnaire and, after the test, the participants received an accelerometer to wear for 7 consecutive days before returning it in a prepaid envelope.

3.6 Outcome measures

3.6.1 Overview of outcome measures

An overview of demographic, OA-related, and health-related variables and measures of physical function, physical activity, and physical fitness are presented in **Table 4**.

Table 4. Overview of demographic, OA-related, and health-related variables and measures of physical activity and physical fitness included in Papers I-IV

	Paper I		**Paper II**	**Paper III**	**Paper IV**	**Description**
	OA	Ref.				
Age	√	√	√	√	√	Years
Gender	√	√	√	√	√	Women/men
Education level	√	-	√	√	√	Primary school, Upper secondary school, 1–4 years of college/university, or ≥4 years of college/university Dichotomized into "Primary/upper secondary school" and "≥1 year of college/university"
Smoking	√	-	√	√	√	**Papers I-II:** Current smoker, Previous smoker, or Never smoked **Papers III-IV**: Yes or No
Living arrangements	-	-	√	√	√	Living alone or Living with someone
Employee status	-	-	√	√	√	**Paper II**: *Currently working?* Yes or No; If no: Student, Retired, Welfare, Sick leave, Other **Papers III-IV**: *Employee status?* Working part time, Sick leave full time, Sick leave part time, Retired, Welfare, Work assessment allowance, Staying at home, or Student Dichotomized into "Working full time" and "Not working full time"
Body mass index	√	-	√	√	√	Body height (in cm) and body weight (in kg) were used to calculate Body mass index (kg/m^2)
Pain/joint pain	√	-	√	√	√	NRS 0-10 (10=worst pain), last week
Fatigue	-	-	-	√	√	NRS 0-10 (10=worst fatigue), last week
Disease activity	-	-	-	√	√	NRS 0-10 (10=very bad), last week
Most troublesome joint	-	-	-	√	√	*Which joint is your most troublesome joint?* Hip (right/left) or Knee (right/left)
Number of troublesome joints	-	-	-	√	√	*Which other joints are troublesome?* Hip (right/left), Knee (right/left), Ankle (right/left), Hand/fingers (right/left)

Comorbidities	-	-	-	√	√	*Is your health currently affected by one or more of these medical problems (Yes or No)?* High blood pressure, Angina/infarction/other cardiac disease, Asthma/bronchitis/other pulmonary disease, Allergy/rhinitis/eczema, Sciatica, Cerebral hemorrhage/cerebral stroke, Cancer disease, Neurological disease (in brain or nerve tissue), Diabetes, Metabolic disease, Mental/psychological disease, Kidney disease, Liver disease, Ulcer or other stomach disease, Anemia or other blood disease
NSAID use	√	-	-	-	-	*Use of glucosamines, paracetamol, or anti-inflammatory pain medication last 7 days*? No, Occasionally, Daily or almost daily Dichotomized into "No/occasionally" and "Daily/almost daily"
Use of pain medication	-	-	-	-	√	*Use of pain medication the last 3 months?* Several times a day, Daily, Weekly, Monthly, Less than monthly, Never Dichotomized into "Daily" and "Less than daily"
Arterial stiffness, resting heart rate	√	-	-	-	-	Carotid-femoral pulse wave velocity (in min/sec) and resting heart rate (in beats/min) assessed by using a SphygmoCor apparatus (Atcor, Australia).
Blood pressure	√	-	-	-	-	Brachial blood pressure was measured after the patient rested for 5 min using an OMRON M7 monitor (Kyoto)
Physical function	√	√	-	-	-	6MWD: measures distance (meters) walked back and forth on a pre-measured indoor, hard, flat surface in 6 min [248]
Physical fitness	-	-	-	√	√	Estimated peak (VO_{2peak}) and max (VO_{2max}) oxygen uptake, based on results on a modified Balke or single stage treadmill test [94, 95, 98].
Objective PA measures	-	-	√	√	√	A hip-worn accelerometer (ActiGraph wGT3X-BT). Assessed over 7 consecutive days.

Subjective PA measures	-	-	√	-	-	IPAQ-SF; Number of days and time walking at moderate and vigorous intensity for at least 10 min duration the last 7 days in addition to sitting time sitting on weekdays the last 7 days Actvity specific questions; *Did you participate in swimming, bicycling/stationary bicycling, resistance exercise (using weights/apparatus) or crossskiing/roller-skiing*? Yes, No or don't know/don't remember; If yes: how many days and average time per day
Joint-related functioning, hip	-	-	-	√	√	HOOS; Normalized scores ranging from 0-100: (0=extreme disability, 100=no disability)
Joint-related functioning, knee	-	-	-	√	√	KOOS; Normalized scores ranging from 0-100: (0=extreme disability, 100=no disability)
Health-related Quality of Life Index	-	-	-	√	√	EQ-5D-5L utility index ranges from -0.59 to 1.00, where a negative value indicates death/worse than death and 1.00 indicates full ("perfect") health [249]
Health status	-	-	√	√	√	Visual analogue scale: 0–100 (0=worst imaginable health, 100=best imaginable health)
Arthritis self-efficacy	-	-	-	√	√	The Norwegian Arthritis Self-Efficacy Scale: subscale sum scores for pain and symptoms ranging from 0–100 (0 = low self-efficacy, 100 = high self-efficacy) [250]
Exercise beliefs and self-efficacy	-	-	-	√	√	The Exercise Beliefs and Exercise Habits questionnaire: on each subscale, a higher score represents better exercise self-efficacy [251]

OA, osteoarthritis; Ref., reference sample; PA, physical activity; NRS, numeric rating scale; NSAID, non-steroidal anti-inflammatory drug; 6MWD, 6-minute walking distance; IPAQ-SF, The International Physical Activity Questionnaire-Short Form; KOOS, Knee Injury and Osteoarthritis Outcome Score; HOOS, Hip Disability and Osteoarthritis Outcome Score.

3.6.2 Physical function

Physical function was measured by the 6-minute walking distance (6MWD) test, which is described as a simple standardized test assessing the submaximal functional capacity [248]. Performing the test involves the cardiovascular, cardiopulmonary, and neuromuscular systems, reflecting an individual's walking endurance and ability to walk over longer distances [86, 101]. Performance on the 6-minute walking test can reflect different constructs related to physical function; thus, the test's validity properties could be interpreted with regard to several constructs. In people with radiographic and symptomatic knee OA, different patient-reported physical function domains have been shown to correlate moderately with 6-minute walking performance (range r=0.46 to 0.52) [252, 253]. In individuals with medial compartment knee OA, 6-minute walking performance correlated moderately with lower limb strength (hamstring or quadriceps; r=0.47) [254]. Furthermore, 6-minute walking performance has been shown to correlate moderately with VO_{2max} in healthy adults (r=0.49) and in adults with various musculoskeletal conditions (r=0.44) [99, 255]. The test is prone to ceiling effects in individuals with normal or high exercise capacity, as the test is restricted to maximum walking speed, and jogging or running is not allowed [86, 248].

Reliability of the 6MWD test, based on test-retest intraclass correlations (ICCs), is reported to be good to excellent in healthy adults and adults with various musculoskeletal conditions (ICC 0.82 to 0.95) [255-257], and excellent within (ICC 0.93, 95% CI 0.77, 0.97) and between (ICC 0.94, 95% CI 0.90, 0.96) assessors when tested in adults with hip or knee OA [258]. A measurement error (standard error of measurement, 95% CI) of 18 meter (15 to 22) has been reported in adults with hip or knee OA, along with a minimum detectable change of 50 meter [258].

3.6.3 Arterial stiffness

The carotid-femoral pulse wave velocity (PWV) is considered the gold standard measure of arterial stiffness [259-261]. The PWV is an index of regional arterial stiffness in the central arteries; a higher speed (meter/second) indicates stiffer arteries and underlying arthrosclerosis [259, 261]. Arterial stiffness is described as a surrogate measure of CVD risk and has been shown to be a strong predictor of cardiovascular events and all-cause mortality [259, 262]. PWV reference values derived from 1455 healthy individuals increases with age, ranging from mean (±2 SD) 6.5 (3.8–9.2) in those aged 30-39 years to 10.9 (5.5–16.3) in those aged 70

years or older [263]. In 2018, a task force for the European Society of Cardiology and the European Society of Hypertension proposed a carotid-femoral PWV cut-off of >10 as the threshold for asymptomatic hypertension-mediated organ damage [261]. As a gold standard measure, the PWV is considered valid, and for reliability, excellent ICCs of 0.940 to 0.976 between three repeated measures are reported [264].

3.6.4 Physical fitness

Physical fitness (VO_{2peak}) was estimated based on performance on an indirect, maximal treadmill test [94, 95], which is considered the best measure of VO_{2peak} if direct measurement, the gold standard, is not feasible or available [74]. In addition, VO_{2max} was estimated by use of an indirect submaximal treadmill test [98]. Submaximal testing is less accurate than direct mesures but is approporiate for patients unable or unwilling to perform testing at maximal exertion [74]. In the current thesis, VO_{2peak} (ml/kg/min) was estimated based on incline and speed at the treadmill test's end stage in combination with age and weight using the following equations [95]:

- Women: *17.21 + (0.582 × incline, percent) + (3.317 × speed, km/h) – (0.116 × weight, kg) – (0.099 × age, years)*
- Men: *24.24 + (0.599 × incline, percent) + (3.197 × speed, km/h) – (0.122 × weight, kg) – (0.126 × age, years)*

In healthy men and women (n=4637) with a mean age (±SD) of 49±14 years, a strong correlation exists between the estimated and gold standard-measured VO_{2peak} for women (r=0.85) and men (r=0.87), with an accuracy of 10.5-11.5% (standard error of estimate) [95]. The equation underestimates VO_{2peak} in individuals with high oxygen uptake (>40-50 ml/kg/min) and overestimates it in individuals with lower oxygen uptake (<30-35 ml/kg/min) [95]. The mean (±SD) difference between two repeated gold standard measures of VO_{2peak} is reported to be 0.3±2.4 (or 1.0%±7.4%) for women and 1.0±4.5 (or 2.7%±11.3%) for men [265].

The VO_{2peak} increases with aerobic exercise; a higher increase in VO_{2peak} is reported following high-intensity interval exercise compared to moderate-intensity exercise [266, 267]. In general, a 3.5 ml/kg/min improvement in VO_2 consumption, corresponding to 1 MET, is associated with 13-15% reduced mortality risk and 15-24% reduced risk of CVD [76, 77, 268], but in patients with coronary heart disease, increments of 1 ml/kg/min is associated with 15% decreased risk of death [269]. In patients with axial spondyloarthritis, an improvement in VO_{2peak} of 3.7 (95% CI 2.1, 5.2), accompanied by reduced arterial stiffness and total and abdominal fat, was detected

following a 12-week exercise regimen including twice weekly 4×4 minutes of high-intensity interval exercise [270].

3.6.5 Physical activity

Objective assessment of physical activity was measured using an accelerometer (ActiGraph wGT3X-BT, LLC, Pensacola, FL), which is a tri-axial research-graded accelerometer that records the frequency and intensity of movement, expressed as counts per time unit; a higher number of counts per minute represents a higher intensity of the movement. The ActiLife software (version 6.13.3, ActiGraph, LLC) was used to initialize the accelerometers and to download and process the accelerometer recordings. The recordings were downloaded from the vertical axis in 60-second time intervals, and a valid recording was defined as at least 600 minutes of recording a day for at least 4 days. Count per minute thresholds defined by Troiano et al. were applied to calculate weekly minutes spent on light, moderate, and vigorous intensity physical activity and sedentary time [271]. Time spent on activities in which the accelerometer has limited capability to record intensity (i.e., swimming or bicycling) was collected by self-reporting (Paper II).

In addition, accelerometer measured physical activity was expressed as:

- Total MET-minutes per week; calculated by multiplying light, moderate, and vigorous intensity activity with MET values of 3.3, 4.0, and 8.0, respectively (Paper II).
- Moderate to vigorous physical activity (MVPA)-MET-minutes per week; calculated by summing moderate and vigorous MET-minutes per week (Paper II).
- MVPA-minutes per week; calculated by summing moderate and vigorous minutes per week (Papers II, III and IV).

Among several accelerometers, the ActiGraph is the most validated [272]. In healthy younger adults (20-39 years of age), the accelerometer showed good validity, as reflected by a strong correlation (R^2=0.82, p=0.001) between uniaxial accelerometer counts and energy expenditure measured by calorimetry (ranging from 2.8 to 6.6 MET) during treadmill walking at speeds of 3 to 7 km/h [273]. Several equations have been developed to translate accelerometer counts into estimated energy expenditure, and the different equations have been reported to correlate poorly to strongly with energy expenditure (R^2=0.17 to 0.89) [274]. In healthy adults with an average age of 38±12 years, one equation has been shown to overestimate moderate- and vigorous-intensity activity 45% and 62%, respectively, whereas another count threshold underestimated moderate- and vigorous-intensity activity by 50% and 57%, respectively [275].

Inter-accelerometer reliability is considered to be excellent (r=0.9-1.0) over 1 to 21-day measures [276] and, for responsiveness, the accelerometer is assumed to accurately detect changes in activity as it records acceleration in real time.

Subjective assessment of physical activity was measured using the IPAQ-SF [277], which comprises four items addressing time spent sitting on weekdays and on walking, moderate activity, and vigorous activity the last 7 days. Answers to the questionnaire are used to calculate physical activity energy expenditure, expressed as MET [243]. Walking corresponds to 3.3 MET, whereas moderate- and vigorous-intensity activity correspond to 4.0 MET and 8.0 MET, respectively. The activity MET scores are calculated by multiplying the number of minutes per day by the number of days per week, giving a score in MET minutes per week for walking, moderate activity, and vigorous activity. Summarizing these MET scores can give a measure of the total activity level expressed as total MET-minutes per week [243].

The IPAQ-SF was developed for surveillance of physical activity in general populations and is one the most widely used physical activity questionnaires [89, 277-279]. The IPAQ-SF is reported to have acceptable reliability in the general population [278]. In individuals with OA, a recent study published in 2021 reported that the reliability (ICC 0.62, 95% CI 0.55, 0.71) was below their a priori criteria for adequate reliability (ICC 0.70) but could have been underestimated due to uncertainty as to whether the patients had stable activity levels over the 3-month test-retest period [280]. For validity, the IPAQ-SF both overestimates and underestimates the activity level compared to objective methods [279].

3.6.6 Feasibility and adherence

The overall feasibility aspects of the AktiWeb program were considered according to the MRC framework for complex interventions [190, 195]. The specific variables related to the evaluation of study logistics, patient acceptability of interventional components (Paper III), and adherence to exercise (Paper IV) in the AktiWeb program are shown in **Table 5**. Outcome variables to assess feasibility and adherence were pre-registered at ClinicalTrials.gov (registration no. NCT04084834).

Table 5. Overview of feasibility (study logistics, patient acceptability) and adherence variables included in Papers III and IV.

Study logistics	**Description**
Eligible patients	Proportion of eligible patients enrolled.
Accelerometer recording	Proportion of enrolled patients with valid* accelerometer recordings at baseline.
Treadmill testing	Proportion of enrolled patients completing the maximal treadmill test according to protocol at baseline.
Exercise diary	Proportion of enrolled patients returning an exercise diary. Number of received exercise diaries. Calculated as median (range).
Follow-up data	Proportion of enrolled patients providing follow-up data.
Resources	Time resources used on delivery of the program (exercise program and motivational messages). Calculated as minutes per week per patient (mean, SD). Time resources used by the peer-supporters. Calculated as minutes per week per patient (mean, SD).
Patient acceptability	
Website	Patients' perception of the AktiWeb website usability. System Usability Scale comprising 10 standardized statements, each scored on a 5-point Likert scale (1=very much disagree, 5=very much agree). Calculated as a sum score ranging from 0 (low usability) to 100 (high usability) [281, 282].
Exercise level	Patient satisfaction with the prescribed exercise level the first week. *Was the initial exercise level suitable?* (Too easy, Just right, or Too hard).
Exercise program	Patient perception of understandability of the described exercise program. *How understandable was the exercise programs you received?* (Very easy, Easy, Unsure, Difficult, or Very difficult).
Program components	Patient perception of program components potentially motivating adherence to the exercise program. *To which degree did the following components** motivate you to adhere to the exercise program?* Each component was scored on NRS 0-10 (0=not motivating at all, 10=very motivating).
Adverse events	Registration of adverse events. Recording of patient contact with the project coordinator due to any adverse event. Recorded by a questionnaire at follow-up (by asking if the patients had carried out any type of treatment that resulted in an adverse event) with the option to elaborate. Adverse events reported in the weekly diaries.
Adherence	
Exercise adherence	Indication of the program's efficacy in promoting adherence to exercise and physical activity. Given in weekly numbers of sessions completed according to the prescribed BORG RPE intensity.

SD, standard deviation; NRS, Numeric Rating Scale, BORG RPE, BORG Rating of Perceived Exertion

* Valid accelerometer recording = minimum 4 days with at least 10 hours recording per day.

** Treadmill test prior to the exercise program, consulting a physiotherapist prior to the exercise program, the tailored exercise program, receiving weekly exercise programs, reporting in the exercise diary, receiving motivational messages, and treadmill re-test at follow-up.

3.7 Sample size

In Paper I, The OA sample comprised 479 patients, and the reference sample comprised 235 individuals, which is considered adequate sample size for comparison purposes. In the OA sample, associations between 6MWD and arterial stiffness were examined in a sample of 352 individuals.

A minimum of 50 patients is a "rule of thumb" recommendation when assessing criterion validity [85, 283], whereas a sample of 100 patients could be rated as excellent methodological quality [284]. In Paper II, we recruited 115 patients, and 93 were included in the analyses to assess the criterion validity of the IPAQ-SF.

In Papers III and IV, we aimed to enroll 50 patients. A formal sample size is not established for feasibility studies in which measures other than efficacy outcomes are of interest [285]. Notably, it is possible to calculate sample size in pilot/feasibility studies, but this is only relevant when efficacy outcomes are the main research question [191, 286]. A sample size of 50 patients is somewhat larger than what is reported for other pilot/feasibility studies [287] but, due to the testing of multiple components and involvement of several stakeholders, 50 patients were considered a sufficient sample to allow for a thorough evaluation of the AktiWeb program.

3.8 Statistics

All statistical analyses were conducted using the IBM SPSS Statistics Version 21/25/27 (Armonk, NY: IBM Corp.). The significance level was set to $p<0.05$. The different statistical methods that were applied in the papers are shown in **Table 6**.

Table 6. Overview of statistics used in the different papers in this thesis.

	Paper			
	I	II	III	IV
Descriptive statistics				
Mean and standard deviation (continuous variables)	X	X	X	
Median and 25^{th}-75^{th} interquartile range (continuous variables)		X	X	X
Number and percentages (categorical variables)	X	X	X	X
Difference between groups statistics				
Independent t-test (testing between group differences)	X			
Analysis of variance (ANOVA) Bonferroni post hoc test (testing between multiple groups differences)	X			
Chi-square test (testing between group distribution of categorical variables)		X		X
Mann-Whitney U test (testing between group difference of non-parametric, continuous variables)				X
Difference within group statistics				
Paired sample t-test (to describe the difference within group between time points for continuous variables)			X	
Difference within group, between instruments statistics				
Wilcoxon signed-rank test (testing within group, between instrument differences of non-parametric continuous variables)		X		
Independent t-test analysis (to describe within group, between instrument differences)		X		
Between instrument correlation/agreement				
Spearman's rank test (testing correlation between non-parametric continuous variables)		X		
Bland-Altman plot (visualization of agreement between continuous variables)		X		
Association(s) between independent and dependent variables				
Univariate linear regression (testing of associations)	X			
Multivariate linear regression (testing of adjusted associations)	X			

3.9 Ethics

All projects included in this thesis complied with the ethical principles of the Declaration of Helsinki and were approved by the Norwegian Regional Committee for Medical and Health Research Ethics (REC) and/or the Data Protection Authority. The methodological study (Paper II) was evaluated as a quality assurance project, which falls outside the scope of the REC. The registration numbers from REC and the Data Protection Authority/Officer are given in **Table 7**. All participants included in the papers of this thesis provided written consent prior to entering the respective studies.

Table 7. Registration numbers from the Norwegian Regional (south-east) Committee for Medical and Health Research Ethics (REC) and the Data Protection Authority for approval of studies in this thesis (Papers I-IV).

Paper	REC	Data Protection Authority
I	Ref. no. 2009/812a	Reg. no. 10-2009 DS
	Ref. no. 2009/1703a	
	Ref. no. 2010/1547	
II	Ref. no. 2017/1559 (evaluated)	Reg. no. 17/16918
III	Ref. no. 2018/2198	Reg. no. 00138
IV	Ref. no. 2018/2198	Reg. no. 00138

Ref., reference; Reg., registration

3.10 User involvement

A patient research partner was involved in the MUST study [246] (Paper I). Important user involvement was established in the development of the information leaflets and the physical activity report that patients were offered in Paper II. Extensive and valuable user involvement was ensured in the AktiWeb project (Papers III and IV). An employee from the patient organization and a dedicated patient research partner were involved in developing the project, representing user involvement at both the organizational and individual level. Thus, development of the AktiWeb program was strongly influenced by user involvement.

4 Summary of results

4.1 Paper I

The objectives of Paper I were to explore physical function in people with OA by comparing walking distance between an OA population and the general population. In addition, we explored the association between walking performance and risk of CVD in the OA population.

A total of 479 OA patients and 235 individuals from the general population were included in the comparison of 6MWD, whereas 352 OA patients were included in the analysis of an association between 6MWD and arterial stiffness (PWV, meters/second). In the OA population, the mean age was 63.2 (SD 8.8) years and 72% were female.

The analyses showed that OA patients had shorter 6MWD compared to people in the general population. On average, women with OA walked 54 meters less (535 m vs. 589 m, 95% CI 36, 73, $p<0.001$) and men 49 meters less (593 m vs. 642 m, 95% CI 24, 74, $p<0.001$) than their gender-matched peers from the general population. Furthermore, the age- and gender-stratified results highlighted that the largest difference in walking distance was observed in patients aged 40-49 years.

Linear regression analyses showed that 6MWD was inversely associated with arterial stiffness in patients with OA. In the adjusted analysis, an increase in the 6MWD of 100 meters corresponded to a 0.3 m/s (95% CI 0.1, 0.5, $p=0.001$) reduction in arterial stiffness.

4.2 Paper II

The main objective of Paper II was to assess the criterion validity of subjectively measured physical activity (measured by IPAQ-SF) compared to objectively measured physical activity (measured by accelerometer) in patients with OA.

A total of 115 patients consented to participate, and 93 participants had data on moderate- and vigorous-intensity physical activity measured by both methods. The participants' mean age was 64.8 (SD 8.7) years, and 87% were female.

The analyses showed weak but mostly significant correlations between the IPAQ-SF and the corresponding accelerometer measures (total MET-minutes/week, rho 0.37, p=0.001; MVPA MET-minutes/week, rho 0.32, p=0.002; MVPA minutes/week, rho 0.33, p=0.001; vigorous min/week, rho 0.11, p=0.311; moderate minutes/week, rho 0.28, p=0.008; walking/light minutes/week, rho 0.15, p=0.210), whereas sitting time correlated moderately (rho 0.46, p<0.001). The discrepancy between the IPAQ-SF and accelerometer measures increased with increasing MVPA MET-minutes, MVPA-minutes, and moderate physical activity minutes reported in the IPAQ-SF.

Compared to accelerometer measurement, participants self-reported significantly lower total activity, walking/light activity, and sitting time (total MET-minutes, mean diff. -1616 [95% CI 1137, 2096], p<0.001; walking/light minutes, mean diff. -729 [95% CI 593, 865], p<0.001; sitting hours, mean diff. -1.8 [95% CI 1.1, 2.5], p<0.001), but they significantly over-reported MVPA (MVPA MET-minutes, mean diff. +775 [95% CI 445, 1104], p<0.001; MVPA-minutes, mean diff. +118 [95% CI 53, 183], p<0.001). Furthermore, 57% of patients achieved the recommended ≥150 minutes MVPA per week according to the IPAQ-SF, whereas the corresponding proportion as measured by the accelerometer was 31%.

4.3 Paper III

The main purpose of Paper III was to explore feasibility (study logistics, patient acceptability, and clinical outcomes) of a web-based exercise program delivered by a patient organization to patients with hip and/or knee OA.

Among the 30 patients with baseline data, the mean age was 63.3 (SD 9.5) years and 70% were women. For study logistics, 71% (35/49) of the patients who were considered eligible consented to participate in the program. Thirty patients met for baseline assessments, all of whom (100%) completed the physical activity assessment, and 60% completed the maximal cardiorespiratory exercise test according to protocol. Twenty-seven of the 30 patients (90%) returned a median of 11 (range, 1-12) exercise diaries, and 22 (73%) returned data at follow-up. Delivery of the program was estimated to take a mean 7.3 (SD 1.1) minutes/week per patient.

The patients rated the usability of the website as “acceptable” (System Usability Scale 0-100, median 78 [interquartile range (IQR), 57, 86]). Eighty-six percent reported that the initial exercise level was “just right”, and 82% found that the exercise program was “quite easy/very easy” to understand.

The clinical outcomes were affected by the Covid-19 pandemic, with only eight patients being allowed to be tested before the hospital closed down. However, for the eight patients with complete data, their MVPA increased by mean 16.4 (95% CI 6.9, 25.9, p=0.005) minutes per day, and their aerobic capacity (VO_{2peak}) improved by mean 1.83 ml/kg/min (95% CI 0.29, 3.36, p=0.026). For the 21 patients who completed the follow-up questionnaire, 24-52% had a meaningful improvement across 16 different patient-reported outcomes.

4.4 Paper IV

The main purpose of Paper IV was to explore adherence to the 12-week AktiWeb exercise program and map barriers for completing the exercise sessions.

Among the 30 patients with baseline data, the mean age was 63.3 (SD 9.5) years and 70% were women. Fifty percent of the patients adhered to the exercise program, defined as completion of at least two exercise sessions a week according to the prescribed intensity for 8-12 weeks.

Explorative analyses showed that individuals in the non-adherent group more often lived alone (p=0.011), whereas patients in the adherent group were more active (MVPA, median 19 [IQR 3, 28] min/day vs. 31 [25, 46] min/day) and had higher aerobic capacity ($VO_{2peak/max}$), median 23.7 [IQR 20.2, 30.8] ml/kg/min vs. 29.3 [26.0, 33.2] ml/kg/min).

Sickness was the most frequently reported barrier for completing the exercise sessions. The predefined barriers (*forgot, too tired, joint pain, worried exercise is causing pain/injury, exercise do not help, boring, lack of time or life stress*) were reported to a lesser degree. Barriers related to OA joint pain contributed to less than 10% of all reported barriers.

5 Discussion

5.1 Methodological considerations (Papers I and II)

5.1.1 Study designs

This thesis comprises three different studies, two with cross-sectional design (Papers I and II) and one with a single-arm, pre-post design (Papers III and IV).

In Paper I, the population-based, cross-sectional design suited the aim to explore prevalent functional capacity in terms of 6MWD in individuals with OA and compare that to a reference population. The strength of a population-based, cross-sectional design is that the results can be representative of a broad selection of people with OA. In the OA population, the design allowed for exploring the association between 6MWD and arterial stiffness, but not for analyzing 6MWD as a causal risk factor for arterial stiffness.

In Paper II, the aim was to assess criterion validity of a physical activity questionnaire by comparing concurrent measures of patient-reported and objective physical activity levels. A cross-sectional design is the appropriate methodology for the purpose of the study [85].

Paper III and IV, the single arm, pre-post design allowed for gaining practical experience from conducting the trial, and suited well with the aim of evaluating feasibility, acceptability and adherence aspects. The pre-post design allows for reporting changes in outcomes from baseline to follow-up, but whether the changes were a result of the intervention or other factors that were not measured cannot be concluded.

5.1.2 Study samples and recruitment

A strength of this thesis is that the study samples were drawn from various populations representing a broad spectrum of people with different degrees of OA treated in primary or specialized healthcare. The population-based OA sample of men and women aged 40-80 years recruited from Ullensaker municipality (Paper I) represents the adult and elderly community-dwelling populations with OA, who are typically seen in primary healthcare services. The final study sample was selected in several stages, as 41% of the entire population (aged 40-80 years) responded to the initial survey, and 60% of those who self-reported OA participated in assessment at the hospital (**Figure 9**). The reasons for not responding to the survey are unknown. A selection bias may have occurred that hampers the generalizability of the results,

but the distribution of age, gender, height, weight, and education level did not differ between those who participated in the assessment at the hospital and those who did not participate, which strengthens the generalizability of the results.

At the hospital-based assessments, some participants did not perform the 6-minute walking test and/or undergo a PWV examination to assess arterial stiffness (**Figure 9**). This was mostly due to logistic reasons (i.e., lack of personnel to administer the tests), which reduces the possibility of selection bias. Furthermore, 130 patients with other rheumatic diseases or history of CVD were excluded to obtain a more homogenous OA sample when testing associations between 6MWD and arterial stiffness. Excluding these participants may have hampered the generalizability of the results, but the more homogenous sample strengthens the internal validity. Notably, the reference population was conveniently sampled among volunteers at different sites, including work sites and community centers [247]. The convenient sampling could have potentially led to an overrepresentation of fit individuals, which would compromise the generalizability of the reference values. The reference sample was comparable to a Norwegian national population sample with regard to age, height, weight, and body mass index, as well as smoking habits and activity level in another Norwegian population-based sample, which supports the internal validity and generalizability of the results [288, 289].

Validation of patient-reported measures requires that the assessment is done in a study sample that represents the target population [85]. A strength of the study sampling to assess criterion validity of the IPAQ-SF was that patients were recruited from the patient education course at Diakonhjemmet Hospital (Paper II), representing a real-world setting. Patients recruited in a hospital setting may be characterized by long disease duration and severe symptoms, and as such are probably not representative of OA patients treated in primary healthcare settings. Furthermore, only about half of the participants at the course consented to enter the study, which could introduce a systematic selection bias. The willingness to participate in the study could be hypothesized to reflect a higher awareness of the importance of physical activity. Unfortunately, data are lacking on those who did not participate in the study, which weakens the generalizability of the results. In addition, Norwegian communication skills were applied as eligibility criteria and the patient education course was communicated in Norwegian, which means that the sample does not reflect the ethnic diversity of the Norwegian population [290].

The study population in Papers III and IV were recruited among OA patients referred for surgical consultation; therefore, the sample may be considered representative of patients who

are likely in need of surgical intervention due to severe joint disease. For the purpose of testing feasibility of and adherence to an exercise program, we aimed to include patients with severe disease, assuming that they will benefit from the exercise program but probably also struggle with adherence. As such, the sample in Papers III and IV may be regarded as providing conservative results.

Sample sizes

In Paper I, the OA sample was compared to a reference sample by independent t-test statistics. The comparison of mean values between groups requires large samples, and the sample sizes of nearly 500 patients and 235 individuals in the reference group were considered adequate. In the OA sample, associations between 6MWD and arterial stiffness were examined in a subsample of 352 individuals, which is considered an adequate sample size for conducting univariate and multivariate regression analyses including adjustments with six independent variables based on the "rule of thumb" of 10 cases per variable.

When assessing criterion validity, a "rule of thumb" recommendation is a minimum sample of 50 patients [85, 283], whereas a sample of 100 patients could be rated as excellent methodological quality [284]. A sample of 93 individuals was included in the analyses to assess the criterion validity of the IPAQ-SF (Paper II), which is considered an adequate sample size for the purpose of the study.

In Papers III and IV, we aimed to enroll 50 patients. Although a formal sample size is not established for feasibility studies [285], a sample size of 50 patients was considered adequate to allow for a thorough evaluation of the AktiWeb program. However, the AktiWeb study was strongly affected by the Covid-19 pandemic, and the inclusion and follow-up of patients were limited due to restrictions at the hospital. Despite the pandemic limitations, the feasibility study (Papers III and IV) provides valuable information for further research on the important field of developing sustainable delivery of healthcare.

5.1.3 Data collection

In Paper I, the comparison of 6MWD data between a large OA population and a reference population is considered a strength of the study. Standardization of test procedures is important when conducting clinical physical performance testing [248, 291]. Data on 6MWD were collected by different personnel at different timepoints and locations, which may have influenced the results. For example, it could be hypothesized that patients with OA who are

willing to spend time on hospital-based examinations have poor general health and are interested in healthcare attention. On the other hand, poor health could also be a reason for not wanting to spend time on a hospital-based study, resulting in a sample providing an over-estimation of 6MWD. Nevertheless, concurrent collection of reference values from healthy subjects drawn from the same population as the OA sample could have strengthened the internal validity of our results. However, data collection for both the OA population and the reference population was based on standardized test protocols [246-248], supporting the validity of the results.

In Paper II, the concurrent measurement of physical activity is considered a strength regarding the soundness of the criterion validity results. However, this concurrent measurement may introduce a bias into the measurement, as the accelerometer was measured prospectively and the questionnaire had to be measured retrospectively. Even if the participants were asked to record when the accelerometer was taken on and off each day, we do not know how the participants wore the accelerometer. Participants could forget to wear the accelerometer, take it off during sedentary behavior, or be extra cautious to wear it during activity, which may introduce systematic or random bias. On the other hand, the criteria of at least 10 hours of recording per day for at least 4 days may reflect a large time period of a person's activity behavior and contributes to strengthening the validity of the results. The "Hawthorne effect", in which people become more aware of and change behavior when being observed, could have influenced the accelerometer measures by participants being more active than usual [292, 293]. On the other hand, if the accelerometer measurements were influenced by a "Hawthorne bias", it is likely that this was also reflected in the questionnaire. If the data collection was affected by the Hawthorne effect, it most likely resulted in somewhat higher activity levels than what is representative but, because it could affect both the self-reported and the accelerometer measures, it could be debated as to whether it affects the criterion validity results. Nonetheless, given that activity behavior may vary over time, the concurrent data collection is considered a strength. Overall, the data collection in Paper II is considered methodologically sound, providing valid results.

In Papers III and IV, data collected by the exercise diary were crucial for the 12-week exercise intervention. The weekly data collection using a digital exercise diary is considered a strength of the study, as weekly reporting may reduce recall bias compared to collecting adherence data only at follow-up. However, a challenge is the dependence on patients returning the diaries. In Paper IV, patients not returning the diaries were classified as non-

adherent but, with a lack of diaries, we do not know whether the patient performed exercise or not, which may have led to a misclassification into adherent and non-adherent groups. Furthermore, self-reporting can lead to over-reporting of adherence, and data collection using objective measures of adherence (i.e., by accelerometer or wrist-worn watch) could have given more valid results.

5.1.4 Outcomes

5.1.4.1 Functional capacity and arterial stiffness

In this thesis, the 6MWD was chosen as a proxy measure for functional capacity (Paper I). The 6MWD is a robust measure known to reflect not only walking endurance and the ability to walk over longer distances, but also aerobic capacity [86, 99, 101, 294]. The 6MWD test is a feasible test recommended by OARSI to assess functional capacity in individuals with hip/knee OA [291] and is frequently used in both healthy subjects and patients with OA [101, 295], with the advantage that the results can be compared between different populations. Although the test can be criticized for not reflecting the overall self-perceived physical function [253], walking is a type of activity that is relevant for most people in everyday living and may be particularly important to address in people with lower limb OA.

The 6MWD test is prone to ceiling effects in individuals with normal or high physical fitness, as the test protocol is restricted to walking, and jogging or running is not allowed [86, 248]. Thus, the test may underestimate the true functional capacity in fit people, which should be taken into account when comparing performance in OA patients and the general population. Reliability of the 6MWD test has been shown to vary between different samples [255, 257, 258, 296] but, based on studies in adults with various musculoskeletal conditions and community-dwelling adults with lower limb OA, a measurement error of at least 50 meters should be considered when interpreting the 6MWD results [255, 258].

The PWV measure of arterial stiffness was used as a proxy measure for CVD risk because it is a validated marker and strong predictor of CVD [259, 262] that has been shown to be modifiable with exercise [297]. The PWV is considered a gold standard measure of arterial stiffness, but the assessment requires competent assessors to obtain accurate measures [259, 261, 298]. In Paper I, the PWV assessment was conducted by trained personnel according to a standardized protocol [246], which strengthens the validity of the results.

5.1.4.2 Physical activity

The overarching advantages of physical activity questionnaires is that they are feasible for use in both research and clinical practice, and the disadvantage is that they are prone to recall and reporting bias. The IPAQ-SF was chosen as a self-reporting instrument because it allows for estimation of physical activity energy expenditure (METs), which strengthens the understanding of the results, as physical activity is defined in terms of energy expenditure [63]. Even if the activity items (walking, moderate and vigorous activity) in the IPAQ-SF are supposed to be combined to calculate total MET scores, we chose to also examine each activity item as separate outcomes. It could be argued that the calculation of total MET is based on the scoring of each item and, therefore, is a prerequisite for an accurate estimation of total MET. Examining outcomes for both total MET score and time in intensity-specific activity provides information about the amount of intensity-specific activity that contributes to the total MET score, which strengthens the interpretation of the validity of the measure.

A hip-worn accelerometer was used as an objective criterion to measure habitual physical activity. A hip-worn accelerometer records activity that involves movement of the hip, with the advantage that it can capture ambulatory activities involving large muscle groups, which is likely to reflect the majority of a person's activity-related energy expenditure. On the other hand, increased activity-related energy expenditure caused by, for example, external loading or upper body activity is poorly recorded, which can hamper the validity of the results. We translated the raw data recordings from the accelerometer using previously developed count thresholds to express a patient's time in intensity-specific activity [271]. The threshold above 2019 counts per minute, reflecting moderate-intensity activity, was developed by Troiano et al. based on a weighted average of four different calibration studies, including healthy adults up to 45 years of age [299-302]. The inability of the accelerometer to capture activity not involving hip movement and the count threshold based on calibration studies on healthy, younger adults are considered the two main methodological limitations of the accelerometer measures. Yet, the count thresholds were chosen because they are applied in several epidemiological studies including general populations and populations with OA [78, 79, 271, 303, 304], enabling comparisons of our results to other studies.

5.1.4.3 Feasibility outcomes

In contrast to traditional study outcomes, feasibility outcomes are mainly related to procedural and methodological aspects according to the purpose of feasibility studies [198]. In Papers III and IV, outcomes were based on quantitative data, but adding qualitative data could have

provided information to support the feasibility evaluation. Nonetheless, we collected information for a wide range of outcomes from the start to the end of the study, including recruitment and data collection processes, website usability, compliance with returning the diary, and data collection at follow-up, allowing a thorough and comprehensive evaluation of the program. A limitation is that we did not predefine criteria or thresholds to guide the evaluation of the program. Predefined evaluation criteria would have increased the transparency and validity of our evaluation. On the other hand, the feasibility outcomes were prespecified and registered in advance (ClinicalTrials.gov, registration no. NCT04084834), which strengthens the transparency of the feasibility study.

The participants reported the intensity of each session using the BORG RPE scale in their exercise diaries, which was valuable for evaluating adherence to the exercise program. Although other measures, such as percentage of maximal heart rate, could have been used to indicate adherence to exercise, heart rate can be influenced by medication (e.g., beta-blockers) and requires that heart rate monitoring equipment is available and used accurately. The BORG RPE scale is a feasible and robust measure of a person's perceived exercise intensity, with the limitation that patients' reporting relies on experience and interpretation of the scale. In the AktiWeb study, the patients were familiarized with the BORG scale during the baseline treadmill testing, which may have helped them to report accurately on the scale, strengthening the validity of the exercise adherence results. However, the difference between perceived and measured intensity must still be accounted for when interpreting the adherence results.

In Paper IV, information on exercise adherence was based on the exercise diary asking how many and which of the prescribed sessions were performed, with an additional question asking specifically about the intensity (BORG RPE) of each session, which could help reduce the risk of recall bias. Although other instruments to assess adherence outcome exist, a gold standard method is lacking [305]. Compared to outcomes based only on attendance of a session, a strength of our study is that the prescribed BORG intensity was used as a criterion to determine adherence to each session. The use of at least two sessions a week over a minimum 8 weeks as a cut-off to be categorized in the adherent group can be debated. The cut-off was chosen based on a previous finding in our research group that at least two sessions a week over 8 weeks results in a higher chance of symptom improvement in individuals with lower limb OA [306]. Furthermore, according to the ACSM recommendations, two sessions a week may be sufficient to maintain or improve fitness (depending on fitness status) [74].

Adherence is a prerequisite for obtaining beneficial health effects of exercise, and reporting adherence using the BORG scale is considered a strength within the concept of self-management programs.

5.1.5 Development of the innovative AktiWeb intervention

A main pillar in the development of the AktiWeb program was cooperation with a national patient organization, the Norwegian Rheumatism Association. The collaboration with the patient organization and the direct user involvement by a patient research partner and patient organization representative with experience in the field of *Exercise is medicine* was crucial in the development of the program, ensuring relevance and accuracy.

Innovative and sustainable methods for the delivery of healthcare are urgently requested to meet the needs of large groups of patients living with chronic diseases. Providing a tailored exercise program, that is developed and delivered in cooperation with a patient organization, with support from educated peer-supporters, motivational messages, and individual adjustment of the exercise program is a new utilization of existing resources and an innovative approach to develop sustainable treatment trajectories. Assuming that "only the wearer knows where the shoe pinches", peer support may be a valuable resource that extends health care services.

Digital components in the AktiWeb intervention

According to recommendations for first-line treatment of OA, the AktiWeb intervention included a website providing participants with educational information about OA. The information targeted individuals with OA in general and was not individually tailored, which may limit the relevance and uptake of the web-based information. The format of the web-based information built on the experiences from the *Kom i Form* program and was, therefore, concisely described to make the information easy to find and read. Unfortunately, we have no data on the patients' use of the website. Such information could have indicated whether the web-based information was relevant and informed further development of the website.

Although the initial exercise program was developed based on guidelines [74, 133], the final version was adjusted to start with a lower exercise dosage and the two highest exercise levels (level 4 and 5) barely reached the recommended minimum of 500-1000 MET-minutes per week. It is well known that exercise doses with higher intensity have a better effect on aerobic fitness [74], but on the other hand, improvement requires adherence to the exercise program. The patient research partner advised to adjust the exercise dosage to provide a program that

was achievable for most patients, which most likely contributed to higher adherence. In addition, the patient research partner's advice is supported by the ACSM guidelines, stating that exercise dosages below the recommendations can produce health benefits for untrained individuals, and that progression should follow the principle *start low and go slow* [74]. Importantly, the dose-response effect of moving from little to some activity can produce large health benefits for most people.

The motivational messages to promote uptake and adherence to exercise were developed in Australia using a robust methodology [245]. The convenient translation from English to Norwegian were partially conducted according to guidelines [85]. The messages were not translated back to English to check and adjust for inconsistencies, but two different persons translated them into Norwegian. However, some of the messages did not fit Norwegian nature, climate, or culture. The semi-personalized motivational messages sent to patients each week were based on their reporting of predefined barriers to not completing the weekly exercises, but the barrier option *none of the alternatives apply to me* with the possibility to write in free text was often used for reporting, for example, having the flu, fever, or travelling. Thus, many of the messages were conveniently adapted to provide an appropriate response to the patients. It is possible that messages need to be adapted to be suitable for the Norwegian climate; for example, it is probably more likely to get sick during the winter than the summer. Developing the messages using a proper translation methodology, including cultural adaptations and validation of the messages, can contribute to strengthening the motivational messages as part of the intervention.

5.1.6 Ethical considerations

An important aim of this project was to explore the potential for providing a web-based exercise program and utilizing peer-support for more sustainable delivery and support of first-line treatment in patients with OA. This concept raises some ethical considerations related to providing exercise and patient support as treatment outside a healthcare setting (Papers III and IV). "Medicalization" encompasses several phenomena, but one understanding is "*...a process by which some non-medical aspects of human life become to be considered as medical problems*" [307], raising the question of whether physical activity, exercise, and self-management support (or a combination of these) belong within the healthcare services. Physical activity and exercise are recommended as part of a healthy lifestyle for all people,

but self-management support for patients with chronic diseases is traditionally considered to be healthcare. It is debatable as to whether moving *Exercise as medicine* into a patient organization and utilizing peer support as part of the "medicine" is ethical, but the patient organization self-initiated the *Kom i Form* exercise and healthy lifestyle program, and providing peer-support for people with rheumatic musculoskeletal diseases is already one of the organization's core tasks. The collaboration between healthcare services and patient organizations has the potential to ensure optimal treatment for large groups of people in need of support for long-term exercise, such as by combining healthcare professionals knowledge and clinical experience with the resources and networks of patient organizations.

5.1.7 Statistical considerations

Overall, the statistical methods are considered adequate for the aims in this thesis. In general, statistical analyses in small sample sizes are prone to type II error, but in papers with a small sample size (Papers III and IV) we did not draw any confirmative conclusions based on results from the statistical analyses, as these studies were designed to inform the planning of a future RCT.

The visualization of the agreement between the self-reported and objectively measured physical activity by Bland-Altman plots (Paper II) supports the interpretation of the results and may be considered a strength.

In Paper IV, a logistic regression analysis could have been appropriate to examine whether any background characteristics were predictive or associated with being adherent or non-adherent to exercise. However, due to the small sample size, we compared the differences between the two groups using a simple but appropriate statistical analysis.

5.2 Discussion of results

5.2.1 Functional capacity (Paper I)

Both strengthening and aerobic exercise are core components in first-line treatment for patients with OA, but exisiting treatment programs have so far largely focused on strengthening exercise [117, 125, 126, 181, 183, 187]. In a large population-based OA cohort, we found that men and women with OA had significantly shorter walking distances than a gender-matched reference population. Surprisingly, the largest difference in walking distance was found for the youngest OA group. An observational cohort of 18,490 individuals assessed self-reported walking ability and reported that symptomatic hip and knee OA was the strongest contributor to walking disability [308]. A cross-sectional study reported that individuals with OA spend 8-11 hours a day in sedentary behavior and showed an association between a higher amount of sedentary time and poorer physical function [79]. Other studies have shown that only a few are physically active [78, 80]. Therefore, a focus on aerobic exercise for OA is also important, as improved aerobic capacity may, in turn, improve functional capacity beyond the effects of strengthening exercise.

In Paper I, we found that walking distance was associated with PWV, a measure of arterial stiffness, in the OA group. PWV is regarded as a proxy measure of CVD risk. The cross-sectional design does not allow for deciding a causal relationship between walking distance and arterial stiffness, but the results are supported by evidence from a meta-analysis showing that individuals with OA had an almost three-times higher risk of developing CVD compared to matched non-OA cohorts [51]. Effectively targeting modifiable factors is important for long-term health outcomes. Aerobic exercise and strengthening exercise have been shown to have similar beneficial effects on pain and function [142, 143], but aerobic exercise is superior when it comes to improving arterial stiffness and walking distance [297, 309]. Therefore, including aerobic exercise in treatment programs for OA has a two-fold purpose: improving aerobic capacity and curbing the risk of developing CVD.

In Paper I, we showed that the difference in walking distance between individuals with OA and the general population was significant already from the age of 40 years, and that longer walking distance was inversely associated with PWV. Importantly, both walking distance and arterial PWV are modifiable factors and may be effectively targeted by aerobic exercise. An individually tailored exercise program is *Exercise as medicine* for people with OA, with the potential to produce optimal health outcomes.

5.2.2 Measuring physical activity (Paper II)

Individually tailored exercise programs require instruments that are valid, accurate, and feasible for measuring a patient's activity level. In Paper II, the aim was to examine whether a self-reported subjective physical activity measure (IPAQ-SF) is comparable to objectively measured physical activity using an accelerometer. The main finding was that patients with OA tend to under-report sitting time and activity of lower intensity but over-report activity of higher intensity compared to activity measured by an accelerometer. On average, patients reported participating in 180 minutes of MVPA per week, whereas the accelerometer recorded 60 minutes of MVPA per week. These results are in line with other studies comparing self-reported and objectively measured physical activity [279, 310, 311], indicating that some disagreement between the two methods must be taken into account.

The Bland-Altman plots visualizing the agreement between the two instruments in Paper II revealed that the difference between self-reported and objectively measured physical activity increased with increasing time spent on MVPA. A possible explanation may be that OA-related pain makes movement more strenuous and affects the patient's experience of taking part in physical activities [312, 313]. The observed discrepancy between patient-reported and objectively measured activity is of clinical importance. The patient's experience of being active may give equally relevant information as objectively measured activity when tailoring the exercise program. Pain may be demotivating, making patients reluctant to initiate and adhere to the program. Therefore, clinicians should address patients' pain experience to help them overcome barriers. Based on patient feedback, an action to enhance starting exercise and adherence to the program is to lower the initial exercise dose. Even if low-dose exercise is sub-optimal for beneficial health outcomes, it may be important to help patients get started, thereby enhancing good clinical practice.

5.2.3 The AktiWeb program (Papers III and IV)

When testing out the AktiWeb program, 71% of the eligible patients consented to participate and 86% of these patients met for baseline testing. Some patients declined to participate because they preferred other forms of exercise programs, which confirms that "one size doesn't fit all" and that providing alternative strategies for exercise delivery is important to increase the physical activity level in patients with OA.

For various reasons, 40% of those who met for baseline testing did not perform or complete a maximal treadmill baseline test, but most of them completed a submaximal test instead. Although maximal treadmill testing is the most accurate method for assessing aerobic capacity [74], more easily conducted and available testing methods, such as field-based performance tests and fitness calculators, could replace the maximal test [96, 108, 255]. Such readily available testing methods can possibly lower the threshold for testing in daily clinical practice and facilitate research in large patient groups. Developing and testing the measurement properties of easy, feasible methods for use in clinical practice should be on the future research agenda.

In evaluating the feasibility of the AktiWeb study, we aimed to assess the number of patients attending follow-up testing. However, as scheduled testing had to be cancelled due to the hospitals prioritizing of resources during the Covid-19 pandemic, this was not possible to assess. The participants in the AktiWeb study rated the follow-up treadmill testing as an highly motivating factor for exercise adherence. Therefore, it can be hypothesized that the number of participants attending follow-up testing would have been high in a normal, non-pandemic setting.

Patient information is an important part of management programs and web-based delivery of such information may facilitate easy access to relevant information. The AktiWeb website was rated as acceptable by the participants, supporting that web-based delivery can be a sustainable way of delivering patient information. Although eHealth resources, such as web-based platforms, are recognized to enable sustainable delivery of self-management support [202], a recent meta-synthesis of 21 qualitative studies on people with chronic pain identified limited eHealth literacy and irrelevant content among the barriers to engaging in digitally delivered treatment programs [314]. A reason for the positive rating of the website in the AktiWeb study may be that the information was provided on the website of a patient organization, and that the content and text (written formulations) were developed in close collaboration with patient research partners experienced in communicating patient-relevant information. eHealth literacy is important in future development of digitally delivered treatment programs to ensure that information is available for all groups of people. It is currently a well-known problem that specific groups of people are not represented, as they are excluded from research studies due to a wide range of exclusion criteria (e.g., age, gender, language, function, etc.). Barriers for inclusion can be more or less visible, and further research is important to enlighten the field of eHealth literacy, aiming for equal availability of information and services for all people. An

important aim must be that novel methods for delivery of health information do not introduce additional barriers to inclusion.

Individually tailored and properly dosed exercise is a key component in the management of OA. In the AktiWeb project, the close collaboration with a patient research partner led to an important decision regarding exercise dosages in the program. Based on the patient research partner's strong recommendation, the program dosage was downgraded, and the first three steps of the program were below the ACSM's minimum recommendations [74]. Following the advice from the patient research partner in the AktiWeb project enhanced the accuracy and validity of the exercise program, and close cooperation with those who know "where the shoe pinches" is highly recommended. Although a higher exercise dosage is known to be more effective, patients may need to be familiarized with exercising, and starting with low-dosed exercise may be a strategy to increase adherence. Importantly, in the AktiWeb study, 86% of the participants found the initial exercise level to be just right, underlining the value of patient research partners in the development of exercise programs.

With regard to the presentation of the exercsie program in AktiWeb, particularly the written information and illustrations on the website, 82% of the participants reported that the program was easy or very easy to understand. In cooperation with the patient organization, we put effort into describing the exercise sessions thoroughly. Small, plain language text pieces and illustrated examples to visualize the exercise sessions were used, informing patients on *what to do*, *why do it,* and *how to do it,* which is recommended to make web-based health information understandable for all [315]. The positive findings further emphasize the value of patient research partners in the development of written information.

Due to the Covid-19 pandemic, only a few of the AktiWeb participants took part in the cardiorespiratory fitness test at follow-up, but improvements were still found in cardiorespiratory fitness and physical activity. Our positive results are in contrast to findings of other exercise studies on patients with OA, which failed to find increased objectively measured physical activity levels [316, 317]. The discrepancy between our results and others can be explained by the interventions in other studies focusing on general or strengthening exercise [316, 317], whereas the AktiWeb study specifically targeted aerobic exercise. The positive results for fitness and activity are supported by the results on patient-reported outcomes; across all patient-reported outcomes, 24-52% had an improvement large enough to be categorized as a meaningful change. The study design and small sample size do not allow firm conclusions to be drawn, but as the participants' daily living was affected by the

pandemic (e.g., restricting access to gym facilities and limiting social contact), we can hypothesize that the results are conservative.

It is well-known that patients with OA may need support in adhering to exercise [189, 224, 233], and peer-support is recognized as a resource to promote and support healthy behavior [217]. Surprisingly, the available peer support was not utilized by the patients in our study. A reason for this may be that the participants received weekly motivational messages, which has been shown to be effective in increasing adherence to home-based strengthening exercise among individuals with knee OA [318], and may have contributed to reducing the need for additional support. Furthermore, study participants found weekly reporting in exercise diaries and receiving exercise programs as a response motivated them to adhere to the exercise program, which may have reduced the need for peer-support. Even if peer-support was not utilized in the AktiWeb feasibility study, provision of such support may be a beneficial long-term strategy and should be examined further.

Adherence to exercise is decisive for optimal management. Even if the pandemic caused some unusual barriers (i.e., closed training facilities), our results in Paper IV are comparable to the adherence rate reported in a physiotherapist-supervised exercise program in which 35% of patients with hip and knee OA did not achieve the recommended exercise dose over the course of 8-12 weeks [306]. The AktiWeb strategy is promising and should be further explored as a sustainable approach to promote exercise adherence.

In Paper IV, the adherent group presented better cardiorespiratory fitness and higher activity levels at baseline. Despite the limitations related to the cross-sectional design, it may be hypothesized that patients with higher activity levels find it easier and are more confident following a digital exercise program compared to patients with lower activity levels. For example, people who are more active may have higher self-efficacy, which empowers their ability to follow an exercise program. Non-adherent patients could potentially benefit from utilizing peer-support or, alternatively, following a supervised exercise program. The findings in Paper IV indicate that patients with lower fitness and activity levels are prone to being non-adherent to exercise, underlining the importance of measuring patients' fitness and activity levels early in the disease course.

Support to overcome barriers for exercising is important for facilitating adherence to exercise [189]. OA-related pain is commonly considered a barrier for regular exercise. Surprisingly, in the AktiWeb intervention, pain was rarely reported as a barrier for exercise adherence. In the

free-text reporting, a high proportion of the barriers were related to sickness (i.e., flu), which could be explained by the Covid-19 pandemic and that the intervention was conducted during the winter in Norway. Importantly, another study reported that barriers did not fit the predefined options, which limits the possibility of providing automated digital motivation messages [318]. Identification of other common barriers could strengthen further development of digital motivational messages. Alternatively, free-text barriers could be used to prompt contact with a peer-supporter.

6 Conclusions, clinical implications and future perspectives

6.1 Conclusions

The following conclusions can be drawn from the research questions in this thesis:

- Already from the age of 40, patients with OA showed significantly shorter walking distance compared to matched peers. Furthermore, in patients with OA, walking distance was significantly associated with arterial stiffness, suggesting that walking ability may be important for the CVD risk profile in patients with OA.

- The correlation between self-reported and objectively measured physical activity was weak. Patients tended to under-report light intensity activity and over-report moderate to vigouros activity. According to self-reported activity, 57% of patients achieved the recommended ≥150 minutes MVPA per week, whereas the corresponding proportion as measured by the accelerometer was 31%.

- A web-based self-management program delivered by a patient organization was found to be feasible, acceptable and safe in patients with hip and knee OA. Improved physical activity, cardiorespiratory fitness and several patient-reported outcomes was found after the 12 week exercise program.

- Half of the patients with hip or knee OA adhered to the web-based exercise program. The most frequently reported barrier to adherence was sickness. Barriers related to OA joint pain was rarely reported as a barrier. Patients with low levels of physical activity and cardiorespiratory fitness may be at risk to be non-adherent.

6.2 Clinical implications and future perspectives

Exercise is the most important medicine for patients with OA. The results in Paper I showed that functional limitations were present already at the age of 40 in patients with OA. Therefore, promoting physical activity and exercise early in the disease course is important, both to limit functional decline and, not least, to reduce the risk of comorbidities. However, long-term adherence to exercise as treatment is undoubtedly demanding for many patients. Thus, the idea of this thesis grew out of an interest to explore innovative and sustainable strategies enabling support to patients in self-managing their disease.

Exercise provided as medicine requires individual adaptation of the program, including adjustment of the dosage over time, and tight follow-up to ensure long-term adherence, which in turn require feasible measuring tools. When patients self-report their activity, they tend to over-report activity of higher intensity and under-report sedentary time. This is an important finding, both for clinical practice and for further research. Several easily available methods for measuring an individual's activity have emerged the last years, such as for example smartphone-based accelerometers and applications, many providing extensive information about an individuals health and activity. In addition to examining feasibility and validity of eHealth technology in clinical practice, the broad specter of etical questions in this field should be put on the research agenda in the years to come.

A web-based, peer-supported model for delivery of individually adopted exercise programs was tested for feasibility in the AktiWeb project. The idea was based on the belief that patients have a unique competence in supporting and motivating other patients and may serve as a powerful and continued source of support for patients in need of long-term adherence to exercise. The close collaboration with the patient organization and patient research partners in this project was decisive for the design, the content and the delivery of the program, underlining the necessity of involving patients in research concerning their everyday life. Based on the results of this study, patient organisations may serve as valuable resource for some patients, meeting their need for support. Further research is needed to get more insight in how peer support can be utilized as an extention of health care service. Building on the results of the AktiWeb feasbibilty-study, a full scale, high quality RCT can be carried out, possibly bringing forward results of importance both for patients with OA and for future health care service.

7 References

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8 Papers I-IV

Paper I

I. Joseph KL, Hagen KB, Tveter AT, Magnusson K, Provan SA, Dagfinrud H. Osteoarthritis-Related Walking Disability and Arterial Stiffness: Results From a Cross-Sectional Study. Arthritis care & research. 2019;71(2):252-8.

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AMERICAN COLLEGE OF RHEUMATOLOGY
EDUCATION • TREATMENT • RESEARCH

Arthritis Care & Research
Vol. 71, No. 2, February 2019, pp 252–258
DOI 10.1002/acr.23697

ACTIVITY AND THE RHEUMATIC DISEASES

Osteoarthritis-Related Walking Disability and Arterial Stiffness: Results From a Cross-Sectional Study

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Objective. To compare the 6-minute walking distance (6MWD) in a population-based cohort of patients with osteoarthritis (OA) with that in matched peers from the general population, and to explore the associations between walking ability and risk of cardiovascular disease (CVD) in the OA cohort.

Methods. This cross-sectional study included individuals (ages 40–80 years) who had self-reported OA (n = 500) in a previous population-based study and age- and sex-matched peers from the general population (n = 235). Clinical examinations of the patients with OA included classification according to the American College of Rheumatology criteria, blood sampling, and measuring arterial stiffness (PWV; pulse wave velocity). Group differences in the 6MWD were calculated with *t*-tests. The association between walking ability and CVD risk in the OA cohort was examined using multivariate regression models.

Results. In the age-stratified analyses, the largest mean difference in the 6MWD was observed in the youngest age groups (40–49 years); female patients in the OA group walked 84.6 fewer meters compared with the reference group (579.4 meters and 663.9 meters, respectively; $P < 0.001$), and male patients walked 88.3 fewer meters compared with the reference group (619.9 meters and 708.3 meters, respectively; $P = 0.001$). In the OA group, the 6MWD was significantly associated with PWV in the adjusted analysis ($P = 0.001$); an increase in the walking distance of 100 meters corresponded to a reduction in PWV of 0.3 meters/second.

Conclusion. Even at age 40 years, patients with OA had a significantly shorter mean walking distance compared with their matched peers, underlining the importance of an early clinical approach to OA. Furthermore, in the OA group, the 6MWD was significantly associated with arterial stiffness, suggesting that walking ability is important for the CVD risk profile in patients with OA.

INTRODUCTION

The results of recent systematic reviews (1,2) and population-based cohort studies (3–5) indicate that osteoarthritis (OA) is associated with an increased risk of cardiovascular disease (CVD). Fernandes and Valdes (6) recently reported risk factors shared by both conditions, including age, obesity, chronic inflammation, treatment with nonsteroidal antiinflammatory drugs (NSAIDs), physical inactivity, and walking disability (6). Patients with hip OA and those with knee OA tend to avoid painful physical activity, resulting in walking disability and physical inactivity (7–9), which in turn result in reduced cardiorespiratory fitness. Because cardiorespiratory fitness is an important independent predictor of CVD (10,11), OA may be considered to be an indirect cause of CVD (3,4,6). The co-existence of OA and CVD reinforces the negative health impact and increases the disease burden (6,12).

No cure for OA is available; therefore, it is important to identify modifiable factors that can contribute to limiting negative long-term consequences. Even if the underlying mechanisms for the association between OA and CVD are not fully elucidated, it seems clear that OA-related disability increases the risk of CVD beyond what can be explained by common risk factors such as aging and obesity (6). Arterial stiffness is a validated marker of the risk of cardiovascular events and a predictor of mortality (13,14).

The Musculoskeletal pain in Ullensaker STudy was funded by the South-Eastern Norway Regional Health Authority Osteoarthritis Research Group, the Anders Jahre Humanitarian Foundation, the Dr. Trygve Gythfeldt and Wife's Research Fund, and the Norwegian Rheumatism Association Research Fund.

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Submitted for publication October 20, 2017; accepted in revised form May 15, 2018.

SIGNIFICANCE & INNOVATIONS

- Individuals with OA have a high risk of cardiovascular disease (CVD), and co-existence of the 2 disorders reinforces and increases the disease burden.
- Walking disability measured by a standardized 6-minute walking distance test was significantly associated with arterial stiffness, which is an independent risk factor for cardiovascular disease.
- The results emphasize the importance of an early and broad clinical approach to OA, addressing prevention and management of CVD risk along with treatment of joint-related symptoms.

An inverse association between the level of physical exercise and arterial stiffness has been observed in healthy individuals as well as in patients with chronic diseases (15,16), indicating that arterial stiffness can be modified with exercise. The performance-based 6-minute walking distance (6MWD) is known to be a valid measure of walking (dis)ability and cardiorespiratory fitness. The aim of this population-based study was to compare the 6MWD in patients with OA with that in age-matched peers from the general population, as well as to explore the association between walking ability and CVD risk as measured by arterial stiffness.

SUBJECTS AND METHODS

Study design and population. This cross-sectional study was part of the Musculoskeletal pain in Ullensaker STudy (MUST), a population-based study in a rural community in Norway, in which musculoskeletal pain was examined (17). Initially, 12,155 inhabitants ages 40–80 years in Ullensaker municipality were invited to participate in a postal survey (questionnaire 1), which was mailed at 3 time points (March 2010, November 2010, and September 2011). Responders who self-reported OA based on the question "Have you ever been diagnosed with osteoarthritis in hip/knee/hand by a medical doctor and/or x-ray?" and consented (n = 1,019) were invited to participate in medical examinations and physical testing at Diakonhjemmet Hospital, Oslo, Norway, and to respond to a second questionnaire (questionnaire 2) addressing OA and CVD. The 1-day medical examinations (i.e., radiography and pulse wave velocity [PWV]) and physical testing (6MWD test) were scheduled to be initiated within 2–5 months after mailing the initial postal survey. The protocol, including the project timeline and other methodologic details, has been described previously (17). The MUST study was approved by the Norwegian Regional Committee for Medical and Health Research Ethics (2009/812a and 2009/1703a).

The current study is based on participants who self-reported OA in the initial postal survey and participated in medical examinations and physical testing. We excluded those who reported inflammatory rheumatic diseases (rheumatoid arthritis, psoriasis arthritis, spondyloarthritis, systemic lupus erythematosus) and/or had a history of CVD (Figure 1). The definition of CVD was based on a reported history of myocardial infarction, percutaneous coronary intervention, coronary artery bypass surgery, cerebral insult or transitory ischemic attack, or angina pectoris in addition to patient-reported pain relief with nitroglycerine.

OA classification criteria and clinical features. At the time of the physical examination, participants were screened for OA, as classified using the American College of Rheumatology (ACR) criteria (18–20). Conventional bilateral radiographs of the hip, knee, and hand joints were obtained, and blood samples were drawn, according to a previously published protocol (17).

In the current study, hip OA was classified according to clinical, laboratory, and radiography criteria (18). The presence of joint space narrowing (superior or medial) and osteophytes (femoral or acetabular) in the hips was determined by a grade of ≥1 according to the Osteoarthritis Research Society International atlas criteria (21). Knee OA was classified according to clinical and radiography criteria (20). A Kellgren/Lawrence grade of ≥2 was used to determine the presence of osteophytes in the knees (22) (1 participant with missing knee radiographs was classified according to clinical criteria). Hand OA was classified according to clinical criteria (19).

Based on fulfillment of the ACR criteria, we created the following 3 OA phenotypes: 1) hand OA (unilateral or bilateral), 2) hip/knee (lower extremity) OA (unilateral or bilateral in hip and/or knee), and 3) non-ACR–classified OA (OA not fulfilling the ACR classification criteria). Joint pain (average pain last week) was self-reported during clinical examinations, based on a numerical rating scale (NRS) ranging from 0 (no pain) to 10 (unbearable pain).

Walking ability. Walking ability in individuals who self-reported OA was determined by the performance-based 6MWD test. The test was administered by physiotherapists, performed according to the American Thoracic Society statement guidelines, and measured in meters (23), and allowing use of walking aids (e.g., canes).

Reference values for the 6MWD. Reference values for the 6MWD were based on individual-level data from a general population, including men and women, ages 18–90 years (n = 370). The cohort was initially established for the purpose of providing reference values for health-related physical fitness measures in patients with musculoskeletal disorders. Participants were recruited from several settings (e.g., work, college/university, community centers for older adults), networks, and locations (e.g., urban, suburban, rural) to achieve a representative sample (mean reference values for 6MWD stratified by age group and sex have been reported previously [24]). In the current study, data for participants in the same age range as

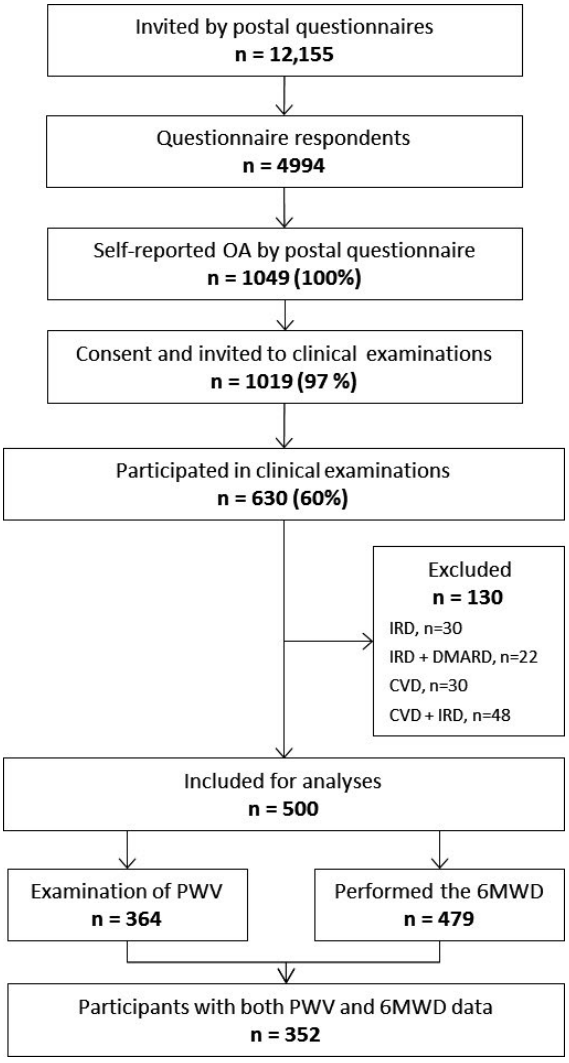

Figure 1. Flow chart showing creation of the population-based osteoarthritis (OA) cohort. IRD = rheumatic inflammatory disease; DMARD = disease-modifying antirheumatic drug; CVD = cardiovascular disease; PWV = pulse wave velocity; 6MWD = 6-minute walking distance.

that in the OA cohort (40–80 years) was used for a comparison of the 6MWD between OA patients and the general population (n = 235).

Arterial stiffness. Arterial stiffness was determined by measuring the PWV (17). The pulse wave between the carotid and femoral arteries and the resting heart rate were assessed using a SphygomoCor apparatus (Atcor). Brachial blood pressure was measured after a 5-minute rest, using an OMRON M7 monitor (Kyoto) according to the MUST protocol (17).

Background variables. Background variables included age, sex, smoking habits (daily, quit >6 months ago, never), education level (primary school, upper secondary school, 1–4 years of college/university, >4 years of college/university), and NSAID use over the last 7 days (no, occasionally, daily/almost daily) (17). NSAID use reported in questionnaire 1 was cross-checked against use of medication reported in questionnaire 2 (recorded by a study nurse) and was categorized accordingly.

For analytic purposes, background variables were collapsed into dichotomous responses: smoking habits (current smoker versus former smoker/never smoker), education (primary/upper secondary school versus ≥1 year of college/university), and NSAID use (no/occasionally versus daily/almost daily). Body height (cm) and weight (kg) were measured and recorded by trained personnel, and the body mass index (BMI) was calculated as kg/m^2.

Statistical analysis. Descriptive characteristics of the participants are shown as the mean ± SD (continuous data) or frequencies and percentages (categorical data). Differences in the 6MWD between patients in the OA cohort (n = 479) and age- and sex-matched peers from the general population (reference group) (n = 235) were analyzed by *t*-test for independent samples. Subgroup analyses to determine the mean difference (sex-matched) in the 6MWD between 1) the OA phenotype groups (hand OA, lower extremity OA, and non–ACR-defined OA) and 2) between OA groups and the reference group were performed using analysis of variance with the Bonferroni post hoc test.

Participants with data for both the 6MWD and PWV were included in the regression models (n = 352) (Figure 1). Univariate analysis was performed to examine the association between arterial stiffness (PWV) (dependent variable) and the 6MWD, resting heart rate, mean arterial blood pressure, age, sex, BMI, smoking, NSAID use, pain (on a numerical rating scale), and OA phenotypes as independent variables, using linear regression models (data not shown). Heart rate, mean arterial blood pressure, age, and sex were forced into the models, and independent variables with a *P* value of less than 0.25 were added to the final model. The final model included only patients with OA who fulfilled the ACR classification criteria. Results for the 6MWD test are presented as unstandardized coefficients (B) and 95% confidence intervals (95% CIs). Data were analyzed using IBM SPSS version 21.

RESULTS

In total, 630 (60%) of the participants who self-reported OA in the MUST study (n = 1,049) participated in clinical examinations and physical testing (Figure 1). No differences were observed between individuals who participated in the clinical examinations and those who did not (n = 419) with regard to age, sex ratio, self-reported height and weight, and educational status.

In the current study, 130 participants were excluded due to inflammatory rheumatic disease (n = 52) and/or CVD (n = 78); thus, 500 individuals were included in the analyses (Figure 1). The mean ± SD time gap between the initial self-report of OA and participation in the medical examinations and physical testing was 8.3

Table 1. Characteristics of the patients in the population-based OA cohort (n = 500)*

Demographics and anthropometrics	
Age, mean ± SD years	63.2 ± 8.8
Female sex	362 (72.4)
BMI, mean ± SD kg/m^2	27.96 ± 4.8
Overweight (BMI 25 to <30 kg/m^2)	183 (36.6)
Obese (BMI ≥30 kg/m^2)	159 (31.8)
Current smoker	80 (16.1)
Education level ≥1 year college/ university	146 (30.0)
ACR-defined OA	
Hand OA	189 (37.8)
Lower extremity OA	158 (31.6)
Non–ACR-defined OA	153 (30.6)
OA-related factors	
Daily/almost daily NSAID use	121 (24.3)
Joint pain on 0–10 NRS, mean ± SD	3.7 ± 2.2
Walking ability†	
6MWD, mean ± SD meters	551.4 ± 99.1
Arterial stiffness‡	
Pulse wave velocity, mean ± SD meters/second	8.82 ± 2.06
Mean arterial pressure, mean ± SD mm Hg	100.61 ± 11.45
Heart rate, mean ± SD beats per minute	64.64 ± 10.03

* Except where indicated otherwise, values are the number (%). OA = osteoarthritis; BMI = body mass index; ACR-defined = defined according to the American College of Rheumatology classification criteria; NSAID = nonsteroidal antiinflammatory drug; NRS = numerical rating scale; 6MWD = 6-minute walking distance.
† Only 479 patients were assessed.
‡ Only 364 patients were assessed.

± 4.0 months. The mean age of the participants was 63 years, and the majority (72%) were women (Table 1). More than two-thirds of the participants (68%) were classified as being overweight or obese. Approximately 1 of 4 patients reported using NSAIDs on a daily/almost daily basis. Most patients (78%) reported joint pain as ≤5 on the NRS. In total, 347 participants (69%) were classified as having OA in ≥1 joints according to the ACR criteria. Measures of arterial stiffness (PWV) in the OA group ranged from 4.65 to 18.30 meters/second (Table 1). Due to logistic reasons, PWV data for 136 patients were missing. There were no statistically significant differences in mean age (P = 0.9) or sex distribution (P = 0.14) between patients with and those without PWV measures, but the mean BMI in patients without PWV measures (1.40 [95% CI 0.45, 2.3], P = 0.004) was higher than that in patients with PWV measures.

OA cohort versus a general population cohort. Compared with that in the general population, the 6MWD was significantly shorter in patients in the OA cohort (in female patients with OA, 535.0 meters versus 589.3 meters in age-matched peers in the general population [P < 0.001]; in male patients with OA, 593.8 meters versus 642.9 meters in age-matched peers in the general population [P < 0.001]). In age-stratified analyses, the largest mean difference in the 6MWD was observed in the youngest age group (40–49 years); in this OA group female patients walked 84.6 fewer meters compared with the reference group (579.4 meters and 663.9 meters, respectively; P < 0.001), and male patients walked 88.3 fewer meters compared with the reference group (619.9 meters and 708.3 meters, respectively; P = 0.001) (Figure 2). These differences were attenuated gradually with increasing age increments; in the oldest age group (70–80 years), female patients walked 21.1 meters fewer compared with the reference group (488.8 meters and 509.9 meters, respectively; P = 0.21), and male patients walked 30.9 meters fewer than the reference group (544.6 meters and 575.5 meters, respectively; P = 0.22) (Figure 2).

In subgroup analyses, no significant differences in the mean 6MWD between OA phenotype groups were observed in either women or men (P > 0.9) (data not shown). With the exception of male patients with hand OA (P = 0.196), the walking distance in all of the OA phenotype groups was significantly shorter than that in the (sex-matched) reference groups (P < 0.05) (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23697/abstract).

Walking disability and arterial stiffness (PWV) in the OA cohort. The 6MWD was inversely associated with arterial stiffness after adjustment for heart rate, mean arterial blood pressure, age, and sex (Table 2). Furthermore, the 6MWD remained significantly associated with PWV in the final model, which had additional adjustments for smoking × BMI (interaction) (unstandardized coefficient –0.003; P = 0.001) (Table 2). This finding means that a 100-meter longer walking distance corresponded to a 0.3 meter/second reduction in arterial stiffness. In a sensitivity analysis of the final model including only patients in whom OA was diagnosed according to the ACR criteria, the 6MWD remained significantly associated with PWV (–0.003 meters/second [95% CI –0.005, –0.001], P = 0.007).

DISCUSSION

This study revealed that even at age 40 years, patients with OA had a significantly shorter walking distance (6MWD) compared with that in their age-matched peers in the general population. Furthermore, we also observed a significant inverse association between the 6MWD and arterial stiffness (PWV) in this population-based OA cohort, suggesting that walking ability is an important factor in the CVD risk profile.

Aging is a strong determinant of functional impairment and reduced physical capacity. Functional fitness is known to decline with increasing age, which may explain our findings that the dif-

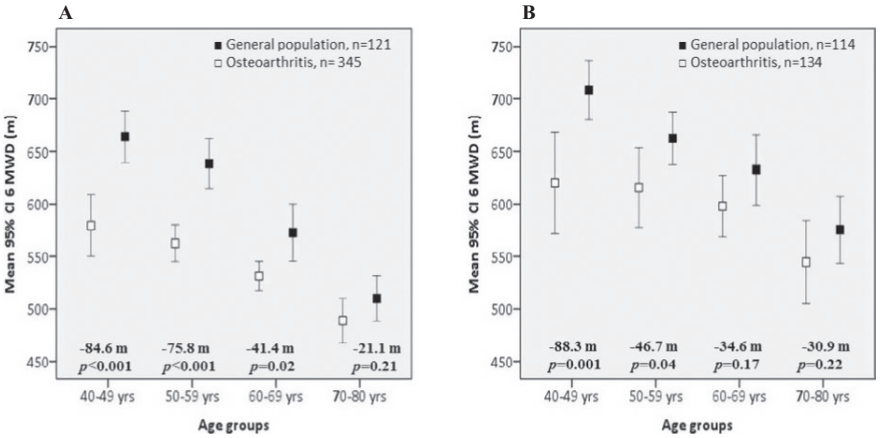

Figure 2. Six-minute walking distance (6MWD) in female subjects (**A**) and male subjects (**B**), according to age group. Values are the means (95% confidence intervals [95% CIs]).

ference in walking distance between the OA groups and age-matched peers was attenuated with increasing age. However, the significant and large differences in the youngest age groups emphasize the importance of an early approach in terms of individually adapted exercise programs, encouragement to stay physically active, and strategies for pain management. Nonpharmacologic treatment modalities are especially important, because the most relevant pharmacologic therapy for management of OA-related pain is use of NSAIDs, which are known to increase the risk of CVD (6,25).

The results of our study support those of previous studies showing that walking disability increases the risk of CVD in patients with OA (3,4). The importance of walking disability was also convincingly emphasized in a recent population-based study of the longitudinal relationship between OA and cardiovascular events (26). Even if OA severity, obesity, and hypertension significantly explained the subsequent risk for cardiovascular events in that longitudinal study, the relationship became nonsignificant when controlling for walking ability at baseline (26). The findings in these previous studies are clinically relevant, because they substantiate the importance of an early approach to treatment of patients with OA. Walking difficulty is a potentially modifiable factor that should be addressed in order to curb the adverse effects of the co-existence of OA and CVD.

The 6MWD test is a feasible clinical field test measuring patients' walking ability, but the test has also been shown to reflect cardiorespiratory fitness ($VO_{2\ max}$) in patients as well as healthy individuals (23,27–29). Burr et al (28) reported a "significant moderate strength association" between the 6MWD and $VO_{2\ max}$ (28) and that in adjusted regression equations, the 6MWD predicted 72% of the $VO_{2\ max}$ variance in healthy subjects (28). In the current study use of the 6MWD to compare patients with OA with their and age- and sex-matched peers increased insight into the early development of walking disability in patients with OA. The shorter walking distance in the OA group may reflect both walking disability and reduced cardiorespiratory fitness, therefore suggesting that treatment strategies should focus on a combination of pain management and cardiorespiratory (not cardiovascular) exercise.

Regular exercise is a prerequisite for maintenance and improvement of cardiorespiratory capacity (30), and walking ability is an important prerequisite for engaging in exercise. However, results from a recent population-based cohort study showed that hip OA or knee OA is a strong contributor to walking difficulty (9), and only a small-to-moderate proportion of patients with hip OA or knee OA meet the guidelines for physical activity (7). Many patients with OA spend a considerable amount of time being sedentary, leading to more impairment in physical function, reduced walking speed (31), and poorer cardiometabolic health (32) compared with their peers who had a less sedentary lifestyle. Therefore, assessment of cardiorespiratory fitness should be prioritized in clinical practice (33), and improved cardiorespiratory fitness

Table 2. Univariate and multivariate linear regression analyses of the association between the 6MWD and arterial stiffness*

	Unadjusted	Model 1	Model 2
B (unstandardized coefficient)	−0.006	−0.002	−0.003
95% CI	−0.008, −0.003	−0.004, −0.001	−0.005, −0.001
P	<0.001	0.007	0.001

* Arterial stiffness was measured using pulse wave velocity (meters/second). Model 1 was adjusted for heart rate, mean arterial blood pressure, age, and sex. Model 2 was adjusted for heart rate, mean arterial blood pressure, age, sex, smoking, and body mass index. The analyses were conducted in 352 participants. 6MWD = 6-minute walking distance (meters). 95% CI = 95% confidence interval.

should be a treatment goal, in order to prevent cardiovascular comorbidity in OA.

Based on results of studies in the general population, it is well known that improvement of cardiorespiratory fitness is associated with a better CVD risk profile and reduced CVD-related mortality (10,11,34). The reduced risk of CVD associated with aerobic exercise is partly attributable to improved vascular hemodynamic function, including arterial stiffness, and PWV is considered to provide clinically relevant information in addition to and beyond the traditional risk factors (15,35). A meta-analysis of 42 studies (n = 1,627 participants) including both healthy individuals and patients at risk for CVD showed that aerobic exercise improved arterial stiffness, and that higher-intensity exercise was associated with a greater reduction in arterial stiffness (15). Importantly, the authors of that review concluded that resistance exercise, alone or combined with aerobic exercise, had no significant effect on arterial stiffness (15), which emphasizes the importance of including aerobic exercise in the treatment program for OA patients.

According to the National Institute for Health and Care Excellence guidelines, radiologic findings are not required for the diagnosis of OA (36). In the current population cohort, participants were included based on self-reported OA even if they did not fulfill the ACR criteria (non–ACR-defined OA) (18–20). The association between the 6MWD and PWV was significant even when individuals who did not fulfill these criteria were included, indicating that self-reported OA is adequate for diagnostic purposes. Furthermore, a reduced walking distance was observed across all OA subgroups compared the walking distance in the matched control groups (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23697/abstract). The consistent findings in subgroup analyses may imply that OA per se, and not only OA affecting the lower extremities, causes a reduced walking distance.

A strength of this study is the comparison of the 6MWD between the patients in the OA cohort and their age- and sex-matched peers from the general population. The 2 cohorts were recruited during the same time period and from adjacent geographic areas. This approach is considered to be advantageous, because significant differences between countries have been reported for 6MWD (37). Other strengths are the comprehensive medical examination of a large population of patients with OA with several OA phenotypes, including the gold standard noninvasive assessment of arterial stiffness (PWV). Furthermore, the validity of the classification of OA subgroups applied in this study, including the group with non–ACR-classified OA, was confirmed by the sensitivity analyses that showed consistent results.

A limitation of our study is the cross-sectional design, which does not allow for conclusions regarding causality. In addition, the well-known association between NSAID use and CVD (25) was not supported by the findings in our study, possibly due to insufficient data with regard to use of NSAIDs.

This study provides new evidence regarding the early impact of walking disability in patients with OA and also underlines the associations between functional fitness and cardiovascular health in these patients. The results reinforce the strength of the guidelines for physical activity and emphasize the importance of an early and broad clinical approach to OA, addressing prevention and management of CVD risk along with treatment of joint-related symptoms.

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 published. Dr. Joseph 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. Joseph, Hagen, Magnusson, Tveter, Provan, Dagfinrud.

Acquisition of data. Hagen, Tveter, Provan.

Analysis and interpretation of data. Joseph, Hagen, Magnusson, Tveter, Provan, Dagfinrud.

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Paper II

II. Joseph KL, Dagfinrud H, Christie A, Hagen KB, Tveter AT. Criterion validity of The International Physical Activity Questionnaire-Short Form (IPAQ-SF) for use in clinical practice in patients with osteoarthritis. BMC musculoskeletal disorders. 2021;22(1):232.

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Joseph et al. BMC Musculoskeletal Disorders (2021) 22:232
https://doi.org/10.1186/s12891-021-04069-z

BMC Musculoskeletal Disorders

RESEARCH ARTICLE Open Access

Criterion validity of The International Physical Activity Questionnaire-Short Form (IPAQ-SF) for use in clinical practice in patients with osteoarthritis

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Abstract

Background: To tailor physical activity treatment programs for patients with osteoarthritis, clinicians need valid and feasible measurement tools to evaluate habitual physical activity. The widely used International Physical Activity Questionnaire-Short Form (IPAQ-SF) is not previously validated in patients with osteoarthritis.

Purpose: To assess the concurrent criterion validity of the IPAQ-SF in patients with osteoarthritis, using an accelerometer as a criterion-method.

Method: Patients with osteoarthritis ($n = 115$) were recruited at The Division of Rheumatology and Research at Diakonhjemmet Hospital (Oslo, Norway). Physical activity was measured by patients wearing an accelerometer (ActiGraph wGT3X-BT) for seven consecutive days, followed by reporting their physical activity for the past 7 days using the IPAQ-SF. Comparison of proportions that fulfilled physical activity recommendations as measured by the two methods were tested by Pearson Chi-Square analysis. Differences in physical activity levels between the IPAQ-SF and the accelerometer were analyzed with Wilcoxon Signed-Rank Test and Spearman rank correlation test. Bland-Altman plots were used to visualize the concurrent criterion validity for total- and intensity-specific physical activity levels.

Results: In total, 93 patients provided complete physical activity data, mean (SD) age was 65 (8.7) years, 87% were women. According to the IPAQ-SF, 57% of the patients fulfilled the minimum physical activity recommendations compared to 31% according to the accelerometer ($p = 0.043$). When comparing the IPAQ-SF to the accelerometer we found significant under-reporting of total physical activity MET-minutes ($p = < 0.001$), sitting ($p = < 0.001$) and walking ($p < 0.001$), and significant over-reporting of moderate-to-vigorous physical activity ($p < 0.001$). For the different physical activity levels, correlations between the IPAQ-SF and the accelerometer ranged from rho 0.106 to 0.462. The Bland-Altman plots indicated an increased divergence between the two methods with increasing time spent on moderate-to-vigorous intensity physical activity.

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Conclusion: Physical activity is a core treatment of osteoarthritis. Our finding that patients tend to over-report activity of higher intensity and under-report low-intensity activity and sitting-time is of clinical importance. We conclude that the concurrent criterion validity of the IPAQ-SF was weak in patients with osteoarthritis.

Keywords: Physical activity assessment, Criterion validity, IPAQ-SF, Accelerometer, Osteoarthritis, Clinical practice

Background

Tailored physical activity (PA) is the cornerstone in treatment of patients with osteoarthritis (OA) [1]. To curb disease specific symptoms like pain and joint stiffness as well as reduce the risk of cardiovascular comorbidities [1–5], PA of moderate-to-vigorous intensity is found effective and is recommended throughout the course of the disease [1, 6–8]. To provide individually tailored PA treatment programs with optimal exercise dosage, clinicians need valid and feasible measures to evaluate their patients' habitual PA level [9]. In clinical practice, the measurement tools must be easy to administer at a low cost and pose minimal patient burden, but still provide valid information.

PA is defined by requirement of increased energy expenditure [10]. PA energy expenditure in free-living environments can be assessed by the gold standard doubly labelled water method, by activity monitors, heart rate monitors, pedometers, diaries or by questionnaires [11]. The doubly labelled water method provides information solely on individuals' energy expenditure [11, 12]. This method does not give information on habitual PA profile in terms of intensity, frequency or duration of the activity, which is important when evaluating patients' PA levels [1]. However, activity monitors such as accelerometers, provide daily profiles on habitual PA [11, 13]. Accelerometers also allow for calculation of PA energy expenditure and weekly time in intensity specific PA (e.g. according to PA recommendations). Accelerometers are shown to agree well with the doubly labelled water method and may therefore serve as a criterion-method for measuring habitual PA [12, 14, 15].

Due to the lack of immediate information on PA from accelerometers, self-report questionnaires are often used in clinical practice. Questionnaires are easy to administer, have a low cost, and pose minimal burden on patients and clinicians, but a challenge is that they are prone to recall- and reporting bias [16, 17]. A questionnaire that is frequently used in research and clinical practice is The International Physical Activity Questionnaire-Short Form (IPAQ-SF) [18–21]. The IPAQ-SF was originally developed and validated for population surveys [22]. The validity of the questionnaire has been assessed in some disease-groups [19], but evidence on criterion validity in patients with OA is lacking [18, 20, 21]. Knowledge about criterion validity is important when assessing PA [20, 21], and in the recommendations for PA in people with OA and inflammatory arthritis the need for valid and feasible methods for assessing PA in clinical practice is underlined [1]. Thus, the purpose of the present study was to assess the concurrent criterion validity of the IPAQ-SF in patients with OA using an accelerometer as a criterion-method.

Methods

Subjects and design

Patients who attended a one-day OA patient education program at The Division of Rheumatology and Research at Diakonhjemmet Hospital (Oslo, Norway) were consecutively recruited from November 2017 to June 2018. Attendance at the program required a referral confirming an OA diagnosis from a doctor at the hospital a or by their general practitioner. Individuals ≥18 years of age, independent of walking aids and competent in verbal- and written Norwegian were eligible for inclusion. Exclusion criteria were patient's incapable of ambulatory movement and/or the inability to understand verbal- and written Norwegian. Eligible patients were given verbal- and written information about the study, and those who provided written, informed consent were included. For excellent methodological quality, a minimum of 100 patients are recommended [23, 24]. To account for possible lack of compliance with using the accelerometer, a total of 115 patients were recruited.

Patients who consented to participate received a study pack including: the IPAQ-SF, an accelerometer, a diary on accelerometer wear-time, an instruction sheet on how to wear the accelerometer and a questionnaire on demographics.

Patients were instructed to wear the accelerometer mounted on the right hip (by an adjustable elastic belt) for all time awake except during water-based activities for seven consecutive days. On day six, a text message was sent to remind the patients to answer the questionnaires either on the seventh day before going to bed or in the morning on day eight, and to return the IPAQ-SF, the accelerometer, the wear-time diary, and the demographic questionnaire. in a pre-paid envelope.

The IPAQ-SF (the international physical activity questionnaire - short form)

The previously translated Norwegian version of The IPAQ-SF (available at www.ipaq.ki.se) was used to assess self-reported PA [22]. The IPAQ-SF addresses the number of days and time spent on PA in moderate intensity, vigorous intensity and walking of at least 10-min duration the last 7 days, and also includes time spent sitting on weekdays the last 7 days [22]. The IPAQ-SF sum score is expressed in PA Metabolic Equivalent of Task (MET)-minutes per day or week. In the present study, data processing and analysis were calculated according to the official IPAQ scoring protocol (www.ipaq.ki.se). Total weekly PA MET-minutes were estimated by adding up the calculated MET-minutes within each PA intensity level (moderate intensity = 4.0 MET, vigorous intensity = 8.0 MET and walking = 3.3 MET). The reported time spent on sitting was calculated as time per weekday. In addition, reported time on moderate and vigorous physical activity (MVPA) were summed and expressed as MVPA-minutes per week and as MVPA MET-minutes per week. Finally, to categorize patients fulfilling or not fulfilling the PA recommendations, MVPA-minutes (≥150 or < 150 MVPA-minutes per week) and vigorous intensity PA (≥75 or < 75 min per week) were dichotomized [1].

The accelerometer

The ActiGraph wGT3X-BT accelerometer (ActiGraph, LLC, Pensacola, FL) was used as a criterion measure of habitual PA. The accelerometer provides data on daily structure of habitual PA over 1–4 weeks, and is a frequently used and validated method [11, 12, 14, 15]. The tri-axial accelerometer continuously records ambulatory movement as counts per minute (CPM) were count-thresholds correspond to different PA intensity levels [13, 25]. Data were downloaded in 1-min time intervals obtained from the vertical axis using the associated licensed ActiLife software (version 6.13.3, ActiGraph, LLC). Valid PA registration was defined as minimum 4 days of at least 10 h of recording per day [25].

Total registration time was defined as 18 h of recording (from 6:00 a.m. to 00:00 a.m.) [26]. Non wear-time was defined as at least 60 consecutive minutes of zero counts (with allowance for ≤2 min with counts below 100), and wear-time was determined by subtracting non wear-time from 18 h [25]. Thresholds for different PA intensities were set to: ≥5999 CPM (vigorous); ≥2020–5998 CPM (moderate); 100–2019 CPM (light) and < 100 CPM (sedentary) [25].

The following calculations were done to make the accelerometer data comparable to the IPAQ-SF outcomes:

1) Total weekly time in different PA intensities was calculated by summing the recorded time within each threshold on valid days (in at least 10-min bouts, allowing for ≤2 min below the respective thresholds), then averaged over number of valid days, and finally multiplied by seven (1 week).
2) Total weekly PA MET-minutes were estimated by applying MET values congruent to the IPAQ-SF MET values, were the corresponding value for moderate intensity was 4.0 MET, vigorous intensity 8.0 MET and for light intensity 3.3 MET. Light activity (100–2019 CPM) was compared to IPAQ-SF walking. Sedentary time on valid weekdays was averaged over valid days and multiplied by 5 (weekdays).
3) Based on these variables, time on moderate and vigorous physical activity (MVPA) were summed and expressed as MVPA-minutes per week and MVPA MET-minutes per week.
4) Finally, to categorize patients fulfilling or not fulfilling the PA recommendations, MVPA-minutes (≥150 or < 150 MVPA-minutes per week) and vigorous intensity PA (≥75 or < 75 min per week) were dichotomized [1].

The diary on accelerometer wear-time (hours on and off each day), included questions concerning activities such as swimming, bicycling/ergometer-cycling, resistance exercise (using weights/apparatus) and cross-skiing/roller-skiing during the measurement week. The answer options on each activity were yes/no/don't know/don't remember (if yes; how many days and average time per day).

Patients demographics

Demographic characteristics were collected by self-report, and comprised age (years), gender, height (cm), weight (kg), smoking habits (current, previous, never), educational level (primary school, upper secondary school, < 4 years college/university, ≥4 years college/university), currently working (yes/no, if no; student, retired, well-fare, sick leave, else), civil status (living alone, living with someone), pain during the last week (Numeric Rating Scale (NRS) ranging from '0' no pain to '10' worst imaginable pain) and general health (EQ-5D visual analog scale ranging from '0' worst imaginable health to '100' best imaginable health). Specific OA joint was not recorded.

Statistics

Data are presented as frequency (n) and proportion (%), mean and standard deviation (SD) or median and interquartile range (IQR, 25th and 75th percentile). Body Mass Index (BMI) was calculated by weight and height

(kg/m^2) and was categorized into normal weight (BMI < 25), overweight (BMI ≥25 to < 30) and obese (BMI ≥30). Data on education level were dichotomized into ≥1 year or < 1 year of college/university. Those reporting 'yes' or 'no' on currently working were categorized as 'employed' and 'not employed', respectively (reporting 'yes' on currently working in combination with 'retired', 'sick leave' or 'else' was categorized as 'employed'). Pain was defined as none to mild pain (NRS ≤5) and moderate to severe pain (NRS ≥6).

In our analyses, we included those with valid accelerometer data and complete data on moderate and vigorous PA by the IPAQ-SF. The difference between the corresponding IPAQ-SF and accelerometer measured PA levels were tested with Wilcoxon Signed-Rank Test. The mean differences and 95% confidence interval (95% CI) that were calculated by independent t-test are shown. Proportions fulfilling the PA recommendations according to the two methods were compared by Pearson Chi-Square analysis.

Concurrent criterion validity of the IPAQ-SF against the corresponding accelerometer measured PA levels was analyzed by Spearman rank test. Correlation coefficients (rho) of ≤0.10 were defined as negligible, 0.10–0.39 as weak, 0.40 to 0.69 as moderate and ≥ 0.70 as strong/very strong [27]. Based on previous studies, we hypothesized weak to moderate correlations between the different PA levels measured by IPAQ-SF and the accelerometer [28, 29]. The mean difference in measured PA levels between the two methods was also visualized by Bland-Altman plots with 95% limits of agreement [30].

Due to the accelerometers' limitations on recording activities such as bicycling, resistance exercises, skiing and swimming (the accelerometer is taken off during water-based activities), we examined if the discrepancy between the two methods in weekly MVPA-minutes were different between patients reporting and not reporting such activities using Mann-Whitney U test. Significance levels were set to $P < 0.05$ in all analyses. Statistical analyses were calculated using IBM SPSS Statistics Version 21.

Results

In total, 105 patients returned valid accelerometer data (Fig. 1), and 96% had five or more valid days with ≥10 h of recording per day. Mean (SD) wear-

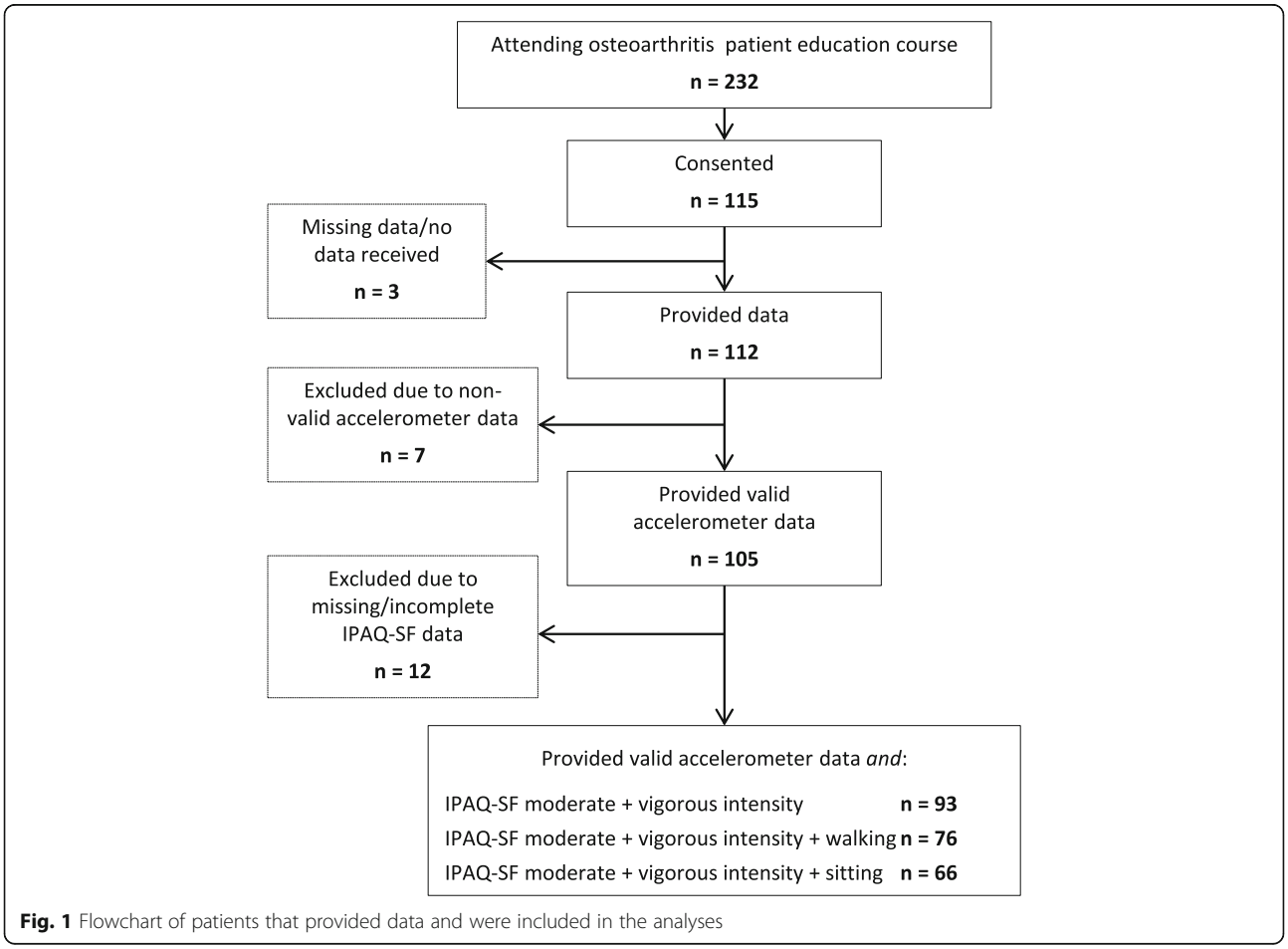

Fig. 1 Flowchart of patients that provided data and were included in the analyses

time was 13.9 (1.2) hours per day. Among patients with valid accelerometer data, 93 (89%) provided IPAQ-SF-data on both moderate and vigorous PA level (Fig. 1). The reasons for missing/incomplete PA data were mostly missing response and/or a 'don't know' response on moderate and/or vigorous intensity in the IPAQ-SF. No statistical differences were found in demographic characteristics between the 93 patients that were included for analyses and the 19 patients that had missing/incomplete PA data (data not shown).

Demographic characteristics are shown in Table 1. Half of the patients (49%) were categorized as overweight/obese (BMI ≥25). Almost one in three (28%) scored moderate to severe pain (NRS ≥6).

More than half of the patients (57.0%) fulfilled the PA recommendations (of minimum 150 min of at least moderate PA per week) according to IPAQ-data, while one in three (31.2%) fulfilled the recommendations according to accelerometer data (Table 2).

When comparing PA levels measured with the two methods, significant differences were found for total PA MET-minutes and all intensity specific PA levels ($p < 0.001$), except moderate intensity ($p = 0.272$). The patients reported lower total PA MET-minutes, less time sitting and walking, and more time in moderate and vigorous PA compared to what was measured by the accelerometer (Table 2). The correlation between PA levels from the IPAQ-SF and the corresponding PA levels from the accelerometer ranged from rho 0.106 to 0.462, were sitting time correlated moderately, and total PA MET-minutes and all intensity specific PA levels correlated weakly (Table 3). The Bland-Altman plots visualized that the difference between the methods increased with increasing minutes of PA for moderate intensity, MVPA-minutes and MVPA MET-minutes (Fig. 2, b, c, e).

Finally, 59 patients reported to spend a median (IQR) of 120 (60, 222) minutes on one or more activities inadequately captured by the accelerometer (cycling, resistance exercises, skiing or swimming). However, for the difference between IPAQ-SF and accelerometer measured time spent on MVPA, no statistical between-group difference was found ($p = 0.560$).

Table 1 Demographic characteristics of patients with osteoarthritis, $n = 93$

Age (years), mean (SD)	**64.8 (8.7)**
Women, n (%)	81 (87.1)
BMI (kg/m2), mean (SD)[a]	25.5 (3.9)
Normal weight (BMI < 25), n (%)	46 (51.1)
Overweight (BMI ≥25 to < 30), n (%)	32 (35.6)
Obese (BMI ≥30), n (%)	12 (13.3)
Smoking, n (%)	
Current	8 (8.6)
Previous	49 (52.7)
Never	36 (38.7)
Education level ≥ 1 year college/university, n (%)	63 (67.7)
Employed, n (%)[b]	42 (46.2)
Not employed status, n (%)	
Retired	37 (40.6)
Well-fare/sick leave/else	12 (13.2)
Civil status, living alone	36 (38.7)
Pain (NRS, 0–10), mean (SD)[c]	4.3 (2.1)
General health (EQ-5D-VAS, 0–100), mean (SD)[b]	64.3 (18.8)

BMI Body mass index; *NRS* Numeric rating scale; *EQ-5D-VAS* EuroQol-5D-Visual Analog Scale; *IQR* Interquartile range.
[a], $n = 90$ due to missing height/weight data to calculate BMI
[b], $n = 91$ due to missing data
[c], $n = 92$ due to missing data

[a], $n = 76$ due to incomplete response on IPAQ-SF.
[b], $n = 66$ due to in incomplete response on IPAQ-SF.
[c], p-value for difference calculated by Pearson Chi-Square analysis.
[d], p-value for difference calculated by two-tailed paired Wilcoxon Signed Ranks Test.
[e], p-value by Wilcoxon analysis not included because calculations resulted in 44 ties with zero vigorous minutes between the IPAQ-SF and the accelerometer.
[a], $n = 76$ due to incomplete response on IPAQ-SF.
[b], $n = 66$ due to incomplete response on IPAQ-SF.

Discussion

In the present study, we compared self-reported physical activity (IPAQ-SF) with concurrent, objectively measured activity (accelerometer) in patients with OA. The main findings were that the patients overestimated self-reported moderate and vigorous activity and underestimated light activity, sitting time and total PA MET-minutes compared to data obtained with the accelerometer.

Based on self-reported PA, we found that more than half of the patients fulfilled the PA recommendations, but only one third of the patients were sufficiently active according to data from the accelerometer. In clinical practice it is important to identify patients that do not fulfill the PA recommendations. However, as our results indicate, these patients may not necessarily be identified by self-reporting their physical activity, which may result in sub-optimal disease management and increased risk of comorbidity.

In our study, we found weak correlations between self-reported and objectively measured total PA MET minutes and the different PA levels. This is in line with results from studies in individuals with self-reported OA [29], hip OA [31], hip- or knee arthroplasty [28] and in the general population [26], showing similar weak to moderate correlations between various self-reported and

Table 2 Physical activity values assessed by IPAQ-SF and accelerometer, including *p*-values for differences ($n = 93$)

	IPAQ-SF	Accelerometer	Mean difference (95% CI)	Difference *p*-value
PA guidelines, n (%)*				
Proportion fulfilling PA guidelines	53 (57.0)	29 (31.2)		0.043[c]
PA levels, median (IQR)				
Total PA MET-minutes, per week	1985 (898, 4217) [a]	4059 (2712, 5467)	− 1616 (− 2096, − 1137)	< 0.001 [d]
MVPA MET-minutes, per week	780 (120,1680)	238 (45, 648)	775 (445, 1104)	< 0.001 [d]
MVPA-minutes, per week	180 (30, 300)	60 (11, 162)	118 (53, 183)	< 0.001 [d]
Vigorous PA, minutes per week	15 (0, 120)	0 (0, 0)	70 (45, 96)	- [e]
Moderate PA, minutes per week	90 (0, 210)	60 (11, 162)	53 (−1, 107)	0.272 [d]
Walking/light PA, minutes per week	245 (105, 630) [a]	1101 (711, 1475)	− 729 (− 865, − 593)	< 0.001 [d]
Sitting/sedentary time, hours per weekday	6.0 (4.0, 10.0) [b]	8.9 (7.8, 10.0)	−1.8 (−2.5, − 1.1)	< 0.001 [d]

95% CI, 95% confidence interval; *IPAQ-SF* The International Physical Activity Questionnaire-Short Form; *MVPA* moderate to vigorous intensity physical activity; *MET* Metabolic Equivalent of Task.
Data given in frequency (percent) for 'Proportion fulfilling PA guidelines' and median (interquartile range, IQR) for 'PA levels'.
*Fulfilling PA guidelines, ≥150 min of MVPA or ≥ 75 min of vigorous PA per week

objectively measured PA levels. Our results underline that PA measures from the two methods cannot be used interchangeably. Important findings of our study were also that participants' under-reported total PA MET-minutes and time spent on light activities, while they reported three times more MVPA-minutes than recorded by the accelerometer. Further, this discrepancy increased with more self-reported time in MVPA. Divergence between the methods can be explained by recall- and reporting bias related to use of questionnaires [16]. For example, walking is an everyday, "unconscious" activity that can be difficult to report in detail, whereas the accelerometer records walking with high accuracy [32]. The underreporting of time spent on walking may indicate that people pay less attention to light, every-day activity than to more intensive activity. Another possible explanation may be that walking is experienced as strenuous in patients with pain and stiffness due to hip- and knee OA, and therefore reported as more vigorous than shown by accelerometer. Since walking is under-reported and MVPA over-reported, the results in our study underline that recording solely total PA minutes is not sufficient when evaluating patients' habitual PA.

Table 3 Spearman correlations (rho) with *p*-values between IPAQ-SF and accelerometer measured PA levels, $n = 93$

PA levels	Correlation	*p*-value
Total PA MET-minutes, per week [a]	0.373	0.001
MVPA MET-minutes, per week	0.315	0.002
MVPA-minutes, per week	0.329	0.001
Vigorous PA, minutes per week	0.106	0.311
Moderate PA, minutes per week	0.275	0.008
Walking/light PA, minutes per week [a]	0.145	0.210
Sitting/sedentary time, hours per weekday [b]	0.462	< 0.001

Pain is a predominant symptom in OA [2], and patients may therefore prefer to engage in moderate to vigorous activities that cause less joint-related pain, i.e. resistance exercises, bicycling or swimming. However, such activities are inadequately recorded by a hip-worn accelerometer. We hypothesized that the type of activity could explain some of the discrepancy between the two methods in our study, but statistical analyses rejected this hypothesis, as no difference in over-reporting of MVPA-minutes was found between those engaging and not engaging in such activities.

In the present study, we found that 57% of the patients fulfilled the PA recommendations based on data from the IPAQ-SF, whereas only 31% was sufficiently active based on data from the accelerometer. Similar results are shown in a population-based OA study, in which half of the patients reported PA levels meeting the recommendations compared to only < 15% according to data from accelerometers [29]. Clinicians must be aware that even if patients report adequate PA, they may not really meet the PA recommendations. Sufficiently dosed PA is shown to be an effective treatment alternative for patients with musculoskeletal diseases, leading to less pain, improved physical function [6–8] and improved cardiorespiratory fitness which in turn is associated with reduced risk of cardiovascular disease [1, 33]. Thus, identifying patients not fulfilling the PA recommendations is important to provide optimal disease management for this large group of patients.

Our study has some limitations. A potential selection bias may be present as patients attending an educational course probably have a more positive attitude towards and are more likely to adhere to treatment

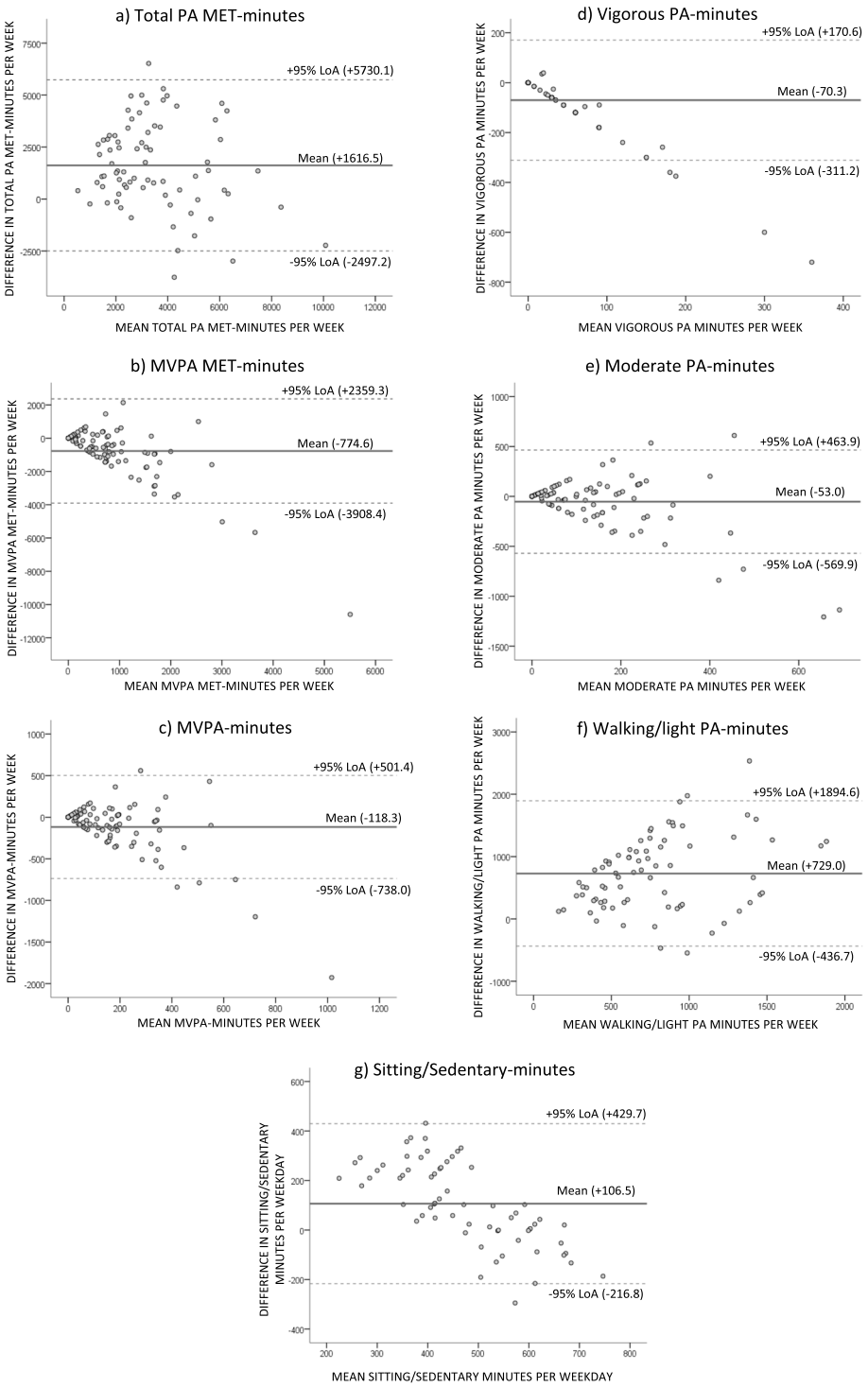

Fig. 2 Bland-Altman plots of the agreement between self-reported PA (IPAQ-SF) and accelerometer measured PA illustrated with mean difference and 95% Limits of Agreement (LoA)

recommendations. Additionally, most of the included patients were women, and the validity of the results for men with OA is therefore unclear. However, the majority of patients with OA are women [29, 34, 35], and the results may thereby be valid for the population seen in clinical practice. Further, we targeted a sample of 100 patients and 93 patient provided sufficient PA data. In rating of methodological quality of studies on

measurement properties it is suggested that samples of 50 is good and 100 is excellent [24]. In our study we analyzed a sample close to 100, and we found no differences in any demographic characteristics between those with and without sufficient PA data. Lastly, the accelerometer used as a criterion-method is not validated in patients with OA [36]. Considering that resting metabolic rate, gender, BMI, and work economy are shown to affect the accuracy of accelerometer measured PA [37, 38], combining accelerometry with heart rate monitoring may improve the accuracy in estimating energy expenditure of habitual PA [39, 40]. Future studies should investigate the accelerometers accuracy in classifying PA intensity in patients with OA, including different subgroups (i.e. OA phenotypes, gender, BMI, age). This is important knowledge in the search for optimal PA dosages in the treatment of OA. But, in lack of a true gold standard to measure habitual PA, accelerometry may be considered the best available single method.

In our study, we found that the patients reported a three-fold more time in high-intensity PA than what accelerometer recordings showed for the same days. An explanation for this could be that experienced intensity may be inflated due to OA symptoms like pain, fatigue or functional limitations. It is previously shown that responses on OA-specific questionnaires are strongly correlated with patients' pain-level, while performance based tests are less influenced by pain [41, 42]. Accordingly, self-report and objective measures of PA do not necessarily provide similar, but rather complementary information, and both methods are needed to better understand the performance and experience of activity in patients with OA. Even if the accelerometer gives more accurate data on habitual activity, the self-report method may capture the patient's experience of being active. This is valuable information for the clinician in helping patients to overcome barriers and motivate for activity as part of the disease management.

Conclusion

We found that correlations between the objective criterion-method and the self-reporting in IPAQ-SF were weak. However, self-reporting PA may capture the patients' experienced intensity of physical activity, which is important for clinicians in providing an optimal PA treatment program. Physical activity dosed according to guidelines is the most important treatment of OA, and the finding that patients with OA tend to over-report activity of higher intensity and under-report low-intensity activity and sitting-time is therefore of clinical importance.

Abbreviations

BMI: Body Mass Index; CI: Confidence Interval; CPM: Counts Per Minute; IPAQ-SF: International Physical Activity Questionnaire-Short Form; IQR: Interquartile Range; MET: Metabolic Equivalent of Task; MVPA: Moderate to Vigorous intensity Physical Activity; NRS: Numeric Rating Scale; OA: Osteoarthritis; PA: Physical Activity; SD: Standard Deviation

Acknowledgements

The authors thank all patients for participating, and the osteoarthritis-course administrator (Liv Skancke and Liv Rognerud Eriksson) for facilitating recruitment of patients.

Authors' contributions

All authors (KLJ, HD, AC, KBH, ATT) made substantial contributions to the study conception and design, drafting and critical revision of the article, and final approval of the submitted version. KLJ and AC contributed to the data acquisition, and KLJ, HD and ATT were responsible for data analyses and interpretation.

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Funding

The study was financially supported by Diakonhjemmet Hospital AS (Oslo, Norway) as employer of the authors (KLJ, HD, AC, KBH and ATT). Accelerometers were acquired by financial support granted by the Klaveness Foundation. The authors of the study initiated and completed the research independently of parties providing financial support.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was carried out in compliance with the Declaration of Helsinki and was evaluated by the Regional Committee for Medical and Health Research Ethics (2017/1559) and approved by a Data Protection Officer at Oslo University Hospital (17/16918). Eligible patients were given verbal- and written information about the study, and those providing written, informed consent were included.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Received: 30 September 2020 Accepted: 10 February 2021
Published online: 27 February 2021

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Publisher's Note

Paper III

III. Joseph KL, Dagfinrud H, Hagen KB, Nordén KR, Fongen C, Wold OM, Hinman RS, Nelligan RK, Bennell KL, Tveter AT. The AktiWeb study: feasibility of a web-based exercise program delivered by a patient organisation to patients with hip and/or knee osteoarthritis. Pilot Feasibility Stud. 2022;8(1):150.

III

Pilot and Feasibility Studies

RESEARCH

Open Access

The AktiWeb study: feasibility of a web-based exercise program delivered by a patient organisation to patients with hip and/or knee osteoarthritis

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Abstract

Background: Patient organisations may be an under-utilised resource in follow-up of patients requiring long-term exercise as part of their disease management. The purpose of this study was to explore the feasibility of a web-based exercise program delivered by a patient organisation to patients with hip and/or knee osteoarthritis (OA).

Methods: In this pre–post feasibility study, patients aged 40–80 years with hip and/or knee OA were recruited from Diakonhjemmet Hospital. The 12-week intervention was delivered through a patient organisation's digital platform. Feasibility was evaluated by proportion of eligible patients enrolled, proportion of enrolled patients who provided valid accelerometer data at baseline, and proportion completing the cardiorespiratory exercise test according to protocol at baseline and completed follow-up assessments. Patient acceptability was evaluated for website usability, satisfaction with the initial exercise level and comprehensibility of the exercise program. Change in clinical outcomes were assessed for physical activity, cardiorespiratory fitness and patient-reported variables.

Results: In total, 49 eligible patients were identified and 35 were enrolled. Thirty (86%) of these attended baseline assessments and provided valid accelerometer data and 18 (51%) completed the maximal cardiorespiratory exercise test according to protocol. Twenty-two (63%) patients completed the follow-up questionnaire, and they rated the website usability as 'acceptable' [median 77.5 out of 100 (IQR 56.9, 85.6)], 19 (86%) reported that the initial exercise level was 'just right' and 18 (82%) that the exercise program was 'very easy' or 'quite easy' to comprehend. Improvement in both moderate to vigorous physical activity (mean change 16.4 min/day; 95% CI 6.9 to 25.9) and cardiorespiratory fitness, VO_{2peak} (mean change 1.83 ml/kg/min; 95% CI 0.29 to 3.36) were found in a subgroup of 8 patients completing these tests. Across all patient-reported outcomes 24–52% of the patients had a meaningful improvement ($n = 22$).

Conclusion: A web-based exercise program delivered by a patient organisation was found to be feasible and acceptable in patients with hip and/or knee OA.

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Trial registration: ClinicalTrials.gov, NCT04084834 (registered 10 September 2019). The Regional Committee for Medical and Health Research Ethics south-east, 2018/2198. URL: Prosjekt #632074 - Aktiv med web-basert støtte. - Cristin (registered 7 June 2019).

Keywords: Osteoarthritis, Follow-up strategy, Patient organisations, Web-based exercise program, Physical activity

Key messages

- The treatment needs of the large group of patients with chronic diseases such as osteoarthritis impose a significant burden on the healthcare system, and patient organisations may be a valuable resource with untapped potential in follow-up of patients requiring long-term exercise as part of their disease management.
- Although some adjustments are needed, a web-based exercise program focusing on cardiorespiratory fitness and delivered through a patient organisation seem feasible, acceptable and safe for patients with hip and/or knee osteoarthritis.
- To provide evidence on the effectiveness of the program, a randomised controlled trial should be conducted.

Introduction

Exercise is a well-documented treatment option for most chronic diseases [1–3], and in line with this, physical activity (PA) and exercise is recommended as first-line treatment for patients with hip and knee osteoarthritis (OA) [4, 5]. It is well known that many patients with hip- and knee OA are less physically active than recommended [6–8], and our recent study showed that at the age of 40, people with OA already had a significantly shorter walking distance on the 6-min walking test compared to an age-matched reference group [9]. Due to increasing life-expectancy in the general population, the prevalence of OA is expected to rise in the next decades [10, 11]. To limit functional decline and development of co-morbidities, this large patient group should be encouraged to include regular exercise as part of their disease management.

Different types of exercise programs (i.e. strengthening and/or aerobic) show similar benefits regarding OA-related symptoms [12], while aerobic exercise also has a particular potential to prevent serious cardiovascular comorbidities which is highly prevalent in OA populations [3, 13]. For beneficial health outcomes, long-term exercise is needed, but adhering to a prescribed exercise program over time is challenging without support [14]. As OA is highly prevalent [15] the treatment needs of patients with OA impose a significant burden on healthcare systems [11, 16]. The development of innovative, scalable and effective treatments and follow-up strategies is urgently required.

Peer-support is recognised as an effective way to strengthen patients' self-efficacy and motivation to support long-term adherence to exercise [13, 14, 17], and patient organisations may be an under-utilised resource in support and follow-up of patients who need long-term exercise as part of their treatment plan. Patient organisations can provide resources such as web-based platforms for interaction and distribution of information, as well as contact with experienced peer-supporters. Web-based delivery of self-management programs, including exercise, is shown to be an effective method for improving pain and physical functioning in patients with musculoskeletal conditions, including OA [18, 19]. Thus, by providing specially adapted exercise programs along with support from a network of experienced and educated peers, patient organisations may fulfil the role of a valuable collaborator and an extended resource for the healthcare service.

In this project, a web-based, peer-supported aerobic exercise program for patients with hip- and/or knee OA (the AktiWeb study) was developed in close cooperation between a patient organisation and physiotherapists and a sport scientist at Diakonhjemmet Hospital. The program was developed as a stepwise, progressive model, in which the exercise dose was individually adjusted based on patients self-reported data in a web-based diary. In order to facilitate further studies on effectiveness and implementation of this model [20], the aim of this study was to explore the feasibility of a web-based exercise program delivered by a patient organisation to patients with hip and/or knee OA.

Methods

Design

This study was a pre-post single-arm feasibility study. The study was evaluated and approved by the Regional Committee for Medical and Health Research Ethics (REK south-east, 2018/2198) and the Data Protection Officer at Diakonhjemmet Hospital (reg. no. 00138). The study was pre-registered in ClinicalTrials.gov (NCT04084834) and recruitment started in October 2019. Reporting of the study follows the Consolidated Standards for Reporting

Trials (CONSORT) 2010 statement: extension to randomised pilot and feasibility trials [21] and the template for intervention description and replication (TIDieR) checklist and guide [22] as appropriate.

Patient recruitment and data collection

Participants were recruited among patients referred to Diakonhjemmet Hospital for surgical consultation due to radiographic hip and/or knee OA. Among patients consulting the surgeon, 49 were pre-screened and identified for possible inclusion. A project associate (CF, AC, KLJ) gave verbal and written information about the study and conducted a more thorough screening against eligibility and exclusion criteria. Inclusion criteria were patients with hip and/or knee OA aged 40–80 years and not considered a candidate for surgery. Exclusion criteria were patients unable to understand or write Norwegian, unable to walk unaided and continuously for 15 min, had relatives with sudden death before 40 years of age, or first-degree relatives with hypertrophic cardiomyopathy or other heart disease, had absolute or relative contradictions to maximal exercise testing (established coronary heart disease and/or symptoms of other heart disease, indication of heart disease during PA, previously confirmed abnormal electrocardiogram measures, systolic blood pressure > 200 mmHg or diastolic blood pressure > 115 mmHg, acute systemic infection with fever, bodily pain or swollen lymph nodes, chronic infection) [23]. Those agreeing to participate provided written consent. Reasons for unwillingness to participate were recorded. Following consent, patients received an URL-link directed to a web-based questionnaire (in Service for Sensitive Data, TSD, University of Oslo, Norway) and an accelerometer to wear for 7 consecutive days before their scheduled baseline assessment at the hospital (within 1–3 weeks). After the baseline assessment, patients initiated the 12-week AktiWeb intervention and were scheduled for a follow-up assessment after 12 weeks. The main study elements are illustrated in Fig. 1.

Sample size

Guidelines for sample size calculation in feasibility studies is not established [21], but it is important that the sample size is large enough to provide sufficient information for running a future randomised controlled trial. In previous studies, sample size in feasibility and pilot studies has been reported to be between 30 and 36 patients [24], while Sim and Lewis [25] have suggested a sample size of at least 50 patients. Due to the multiple components that needed to be tested in the current study (e.g. peer-support, the AktiWeb website, exercise program and exercise diary), we aimed to enrol 50 patients to ensure sufficient data to evaluate feasibility.

The AktiWeb intervention

The AktiWeb intervention was developed in close collaboration between Diakonhjemmet Hospital and a patient organisation (Norwegian League against Rheumatism, NRF). A patient research partner was involved in all phases of the project. The development are according to the newly published UK Medical Research Councils' framework for developing complex interventions [26]. The intervention comprised five components:

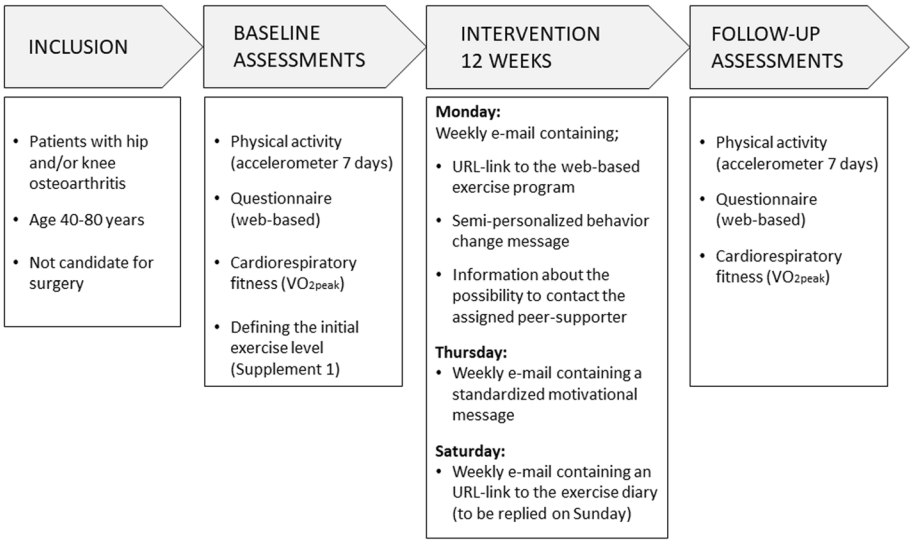

Fig. 1 The main elements of the AktiWeb fesibility study

Peer-support

Two experienced and educated peer-supporters from NRF's network of peers took part in the study. An NRF peer-supporter is a voluntary person with a rheumatic disease who has been educated as a peer-supporter by NRF. The peers' main resource is considered to be the competence to provide knowledge, experience, inspiration, guidance and support related to living with a chronic disease. The patients were reminded weekly via e-mail about the possibility to contact the assigned peer-supporter if needed (the peer-supporters name and mobile number were included). The peers recorded number of contacts and time used per contact.

The AktiWeb website

The website was designed on NRF's official website especially for study participants and contained seven main sections with brief information about recommended core treatment, exercise and symptoms, benefits of exercise, adaption and adjustment of exercise, endurance exercise, PA and the exercise programs. The OA specific information was based on the non-pharmacological treatment recommendations for management of hip- and knee OA [4, 27, 28] and PA recommendations for people with OA [29]. An URL-link to the website was included in the weekly e-mail sent to the patients on Mondays.

The AktiWeb exercise program

The program focused on aerobic exercise and general PA and comprised five different levels with three exercise sessions per week: one interval session, one pyramid interval session and one low intensity session (shown in detail in Additional file 1). Each session was described and graphically illustrated with suggestions on how and where to exercise and included the BORG Rating of Perceived Exertion (RPE) scale to describe intensity [30]. The initial exercise level was defined based on baseline assessments according to predefined criteria including VO_{2peak}, PA habits, pain during activity and experience with interval exercise (shown in detail in Additional file 1), while the exercise level in the following weeks was adjusted by the project manager (ATT) according to responses in the digital diary. If an exercise diary reply was missing the patients received the same exercise program as the previous week. An URL-link to each weekly exercise program were included in the e-mail sent on Mondays. To ensure acceptability and uptake of the exercise program, input from the patient research partner influenced that the initial level was somewhat lower than recommended [29], but with an aim to increase to recommended level during the intervention period.

The exercise diary

Each Saturday, patients received an URL-link to the exercise diary by e-mail in which they were asked to report (on Sunday) the number of exercise sessions performed and if these were completed according to the prescribed program. Patients who completed ≤ 2 of the prescribed sessions were asked to report barriers for not complying with the exercise program. These barriers (forgot, too tired, joint hurts so I cannot exercise, worried exercise is causing pain/injury, exercise is not helping, boring, lack of time, life stress, none of the alternatives apply to me) were adapted from a theory-informed behaviour change message program [31] designed to overcome major barriers to exercise adherence in people with OA [14]. If a reply was missing on Monday morning, the patients received an e-mail reminder.

Motivational behaviour change messages

The patients received unique motivational behaviour change messages twice a week by e-mail; one was standardised to motivate for exercise (i.e. '*Sticking to your exercise program has benefits beyond just your OA*'), while the other was semi-personalized based on exercise diary response and was designed to overcome reported barriers or to reinforce continued exercise adherence (i.e. message related to lack of time: '*Think about what time of day you are less tired. Make a plan to do your exercises at that time of day. Commit to it each week*'). The messages were selected by a project associate (ATT) from a library (198 messages incorporating 20 behaviour change techniques to overcome common barriers to exercise and to facilitate exercise participation) developed by researchers at the University of Melbourne (Australia) according to the Behaviour Change Wheel Framework [31]. The messages were translated into Norwegian and some adjustments were made to fit the aim of the project and to account for seasonal variations in Norway. All weekly e-mails were sent by the project manager (ATT).

Feasibility

Logistics

Feasibility of the logistics was evaluated by calculating proportion of eligible patients enrolled and the proportion of enrolled patients providing valid accelerometer data at baseline, completing the indirect maximal cardiorespiratory exercise test according to protocol at baseline, returning exercise diaries (as well as number of received diaries) and providing follow-up data. The logistics of intervention delivery were evaluated by time used on delivering the intervention (exercise programs and

motivational messages) and time used by peer-supporters (calculated as minutes per patient/week).

Patient acceptability

Patient acceptability of interventional components was evaluated at follow-up by asking the patients about usability of the website, satisfaction with the initial exercise level according to predefined criteria, comprehensibility of the exercise program and the degree to which different components motivated them to adhere to the exercise program.

Clinical outcomes

To inform future studies about relevant clinical outcomes, change in PA, cardiorespiratory fitness and patient-reported outcomes from baseline to follow-up was reported. For patient-reported outcomes, also proportions of patients with meaningful change were reported.

Measures

Website usability was evaluated by using the System Usability Scale (SUS) comprising ten standardised questions, scored on a 5-point Likert scale, which was calculated into a sum score ranging from 0 (low usability) to 100 (high usability) [32] where scores above 70 are considered acceptable usability [33]. Satisfaction with the initial exercise level according to predefined criteria was evaluated by asking patients if the initial exercise level was suitable ('too easy', 'just right' or 'too hard'). Comprehensibility of the exercise program was evaluated by asking if the exercise program was easy to comprehend (5-point Likert scale ranging from 'very difficult' to 'very easy'). The degree to which the different study components motivated the patients to adhere to the exercise program was assessed for seven study components, each scored on an 11-point numeric rating scale (NRS, 0 = was not motivating at all, 10 = was very motivating): performing a treadmill test prior to the exercise program, consulting a physiotherapist prior to the intervention, the tailored exercise program, receiving weekly exercise programs, weekly reporting in the exercise diary, receiving weekly motivational messages and performing a treadmill re-test after 12 weeks.

PA was assessed by accelerometers (ActiGraph GT3X+, Pensacola, FL) prior to baseline assessment and after follow-up assessment at the hospital. Patients were asked to wear the accelerometer on their right hip, using an adjustable elastic belt, during waking hours (except for water-based activities) for seven consecutive days. Data were downloaded and processed (ActiLife Software v6.13.3, ActiGraph, LLC) from the vertical axis in 60-s epochs, and we applied the Troiano algorithm to aggregate data on wear-time, counts per minute (CPM), and moderate to vigorous PA (MVPA, > 2019 CPM) [34].

Cardiorespiratory fitness (VO_{2peak}) was assessed on a treadmill (Woodway PPS55) according to a modified Balke protocol [35]. Age-predicted maximal heart rate [211– (0.64*age)] [36] was estimated, and heart rate was monitored (Polar FT1; Polar, Kempele, Finland) to supervise physiological exertion during the test. Patients rated their perceived exertion using the BORG RPE scale [30]. VO_{2peak} (ml/kg x min) was estimated based on incline and speed at the test end stage in combination with age and weight, using previously developed equations [37]. A submaximal single-stage protocol [38] was prepared for patients unable or unwilling to perform a maximal exercise test. The submaximal test results were excluded from analyses on cardiorespiratory fitness.

Joint-related disability was measured using the Hip disability and Osteoarthritis Outcome Score (HOOS) and Knee injury and Osteoarthritis Outcome score (KOOS) (www.koos.nu). Normalised scores ranging from 0 (extreme disability) to 100 (no disability) were calculated according to scoring instructions (www.koos.nu), and a change of 10 points was considered a meaningful change [39–41].

Numeric rating scales (NRS, 0–10) were used to measure pain (0 = no pain; 10 = worst imaginable pain), disease activity (0 = no symptoms; 10 = very bad), and fatigue (0 = no fatigue; 10 = worst imaginable fatigue) during the last week. A 30% relative change is considered a clinically important change in NRS pain [42, 43], and this was applied to all the NRS scales to define a meaningful change.

The utility index of the EQ-5D-5L (– 0.59 to 1, 1 = perfect health) was used to assess health-related quality of life (www.euroqol.org), using a value set derived from England [44]. Health status was measured with the EQ-5D visual analogue scale (VAS, 0–100, 0 = worst imaginable health; 100 = best imaginable health). For the EQ-5D utility index, a $\geq$ 0.07-point improvement and a $\geq$ 0.05 worsening was defined as meaningful changes and for the EQ-5D VAS, a $\geq$ 10 point change was defined as a meaningful change [45].

The Norwegian Arthritis Self-Efficacy Scale (ASES) was used to assess perceived arthritis specific self-efficacy measured by a pain subscale (5 items) and a symptoms subscale (6 items), each scored on a 5-point Likert scale (1–5) ranging from 'very certain' to 'very uncertain', in which the sum score of each subscale were converted to a 0–100 scale (100 = high self-efficacy) [46].It is recommended to use ASES to assess self-efficacy following patient education programs for people with rheumatic diseases, but responsiveness of the ASES is reported to be poor with standard response means of 0.13–0.19 (<

6%) [47]. Conservatively, we applied a difference of ≥ 10% as an indication of meaningful change.

The Exercise Beliefs and Exercise habits was used to assess exercise self-efficacy measured by four subscales with each item scored on a 5-point Likert scale (1-5) ranging from 'strongly disagree' to 'strongly agree': exercise self-efficacy (4 items, 4–20, 20 = best score), barriers to exercise (3 items, 3–15, 15 = best score), benefits of exercise (5 items, 5–25, 25 = best score), and impact of exercise on arthritis (8 items, 8–40, 40 = best score) [48]. To aid interpretation of the outcomes in relation to the ASES outcomes, we applied a difference of ≥ 10% to indicate a meaningful change.

Participant characteristics

Demographic and clinical characteristics were self-reported and included age, gender, body mass index [kg/m^2], living arrangements [living alone/living with someone], education level [≥ 1 year of college/university (primary school, upper secondary school) and /< 1 year of college/university (college/university < 4 years, college/university ≥ 4 years)], smoking [yes/no], work status [working full time, not working full time (working part time, sick leave full time, sick leave part time, retired, well-fare, work assessment allowance, staying at home, student)], most troublesome joint [right/left, hip/knee], number of troublesome joints [range 1–9, right/left, hip/knee/ankle/hand or fingers], pain [NRS 0–10, 0 = no pain], disease activity [NRS 0–10, 0 = no disease activity] and number of co-morbid conditions [range 0-15, categorised into 0, 1 and ≥ 2 co-morbid condition(s)].

Registration of adverse events

Patients were asked to contact the project coordinator if any adverse event occurred due to the intervention. Adverse events were also recorded by questionnaire at 12-week follow-up and was defined as any adverse event experienced in the last 12 weeks that the patient believed was a result of physical exercise.

Statistical analyses

Data are reported as mean and standard deviation (SD), median and interquartile range (IQR, 25th and 75th percentile) or frequencies and percentage. The change in outcome measures was analysed using paired sample t-test, given as mean change (95% confidence interval), and the proportions of patients with meaningful change and non-meaningful change are shown in percentages. IBM SPSS Statistics version 25 was used for statistical analyses.

Results

Recruitment to the project began in October 2019 and was terminated in March 2020 due to the COVID-19 pandemic and enrolment thus ceased with 35 participants (Fig. 2). Demographics of the enrolled patients with baseline data are shown in Table 1.

Logistics

We identified 49 eligible patients and 35 were enrolled. Among these, 86% (30/35) attended baseline assessments. At baseline compliance with wearing the accelerometer was mean (SD) 6.1 (1.0) valid days with mean (SD) 13.8 (1.3) hours per day. Twenty-nine patients performed a submaximal ($n = 9$) or maximal ($n = 20$) cardiorespiratory exercise test. The peer-supporters were not contacted by the patients. Logistic outcomes are shown in Table 2.

Patient acceptability

The website usability was rated as 'acceptable' with a median (IQR) SUS rating of 77.5 (56.9, 85.6), $n = 22$. Patient satisfaction with the initial exercise level according to predefined criteria was reported to be 'just right' by 19 (86%) patients, 'too easy' by two (9%) patients and 'too hard' by one (5%) patient. The exercise program was found to be 'very easy' to comprehend by 13 (59%) patients, 'quite easy' by five (23%), 'uncertain' by three (14%) and 'very difficult' by one (5%). The degree to which the different study components motivated the patients to adhere to the exercise program are shown in Fig. 3.

Clinical outcomes

In a subset of patients, both PA and cardiorespiratory fitness (VO_{2peak}) increased from baseline to follow-up, and across all patient-reported outcomes 24–52% of the patients reported change in scores that could be categorised as a meaningful improvement (Table 3).

Adverse events

Three patients reported minor events due to transitory pain (back, knee, and unknown site), while one patient reported a moderate adverse event involving consultation with a general practitioner due to chest pain, after which the patient completed the intervention.

Discussion

The main objective of this feasibility study was to examine the logistics and patient acceptability of a 12-week web-based exercise program for patients with hip and/or knee OA. The delivery and follow-up of the program was overall found to be feasible and acceptable,

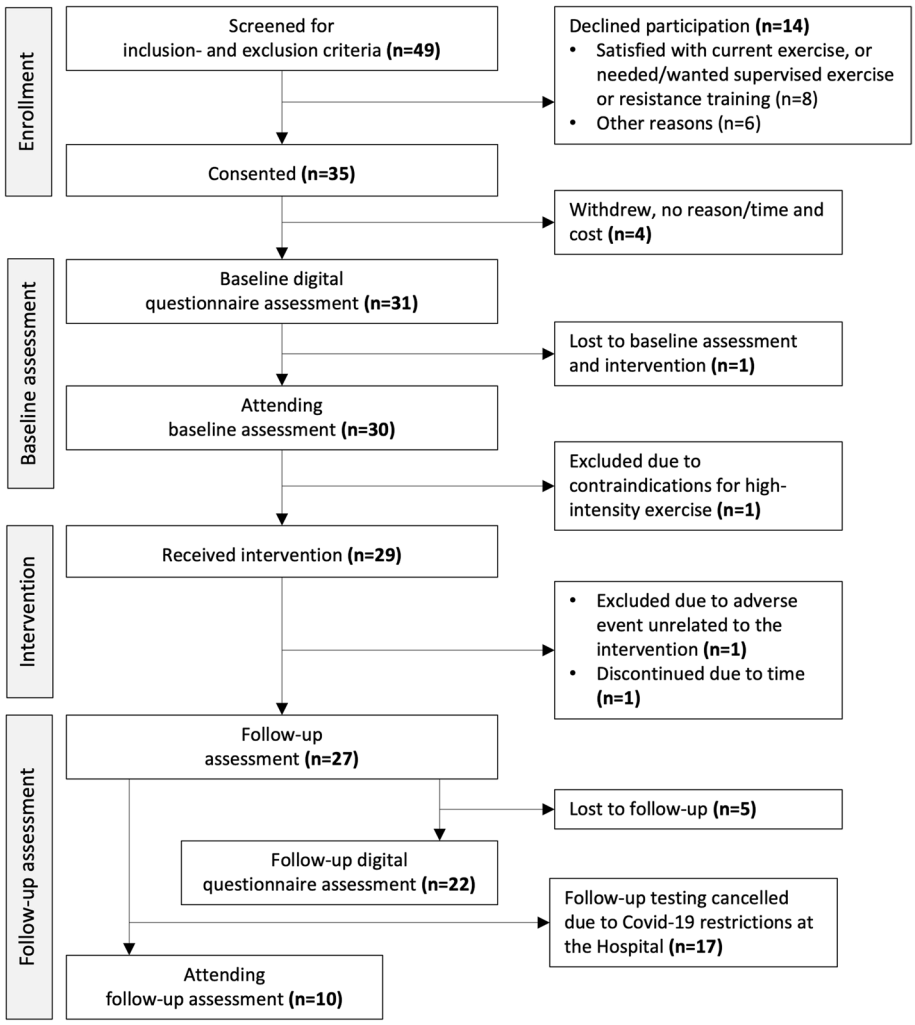

Fig. 2 Flowchart of patient recruitment and data assessments in the AktiWeb study

and a subset of the participants showed improved PA level and cardiorespiratory fitness after completion of the program. Only a few minor adverse events were reported, thus, the intervention is regarded as safe for patients with hip and knee OA. The promising results of this feasibility study can be used for planning a methodologically sound and robust randomised controlled trial.

Innovative follow-up strategies that facilitate patients with chronic conditions to self-manage are needed to support the future healthcare system and patient organisations may be an under-utilised resource in the support and follow-up of patients with OA. Among the resources that patient organisations can offer are web-based platforms for interaction and delivery of disease management programs, as well as access to experienced peer-supporters. In this study, a stepwise, progressive exercise program was developed in close collaboration with a patient organisation, and the program was delivered on their website. This approach showed promising results, indicating that patient organisations can be an alternative pathway of disease management and follow-up for patients with chronic conditions.

The exercise program was delivered on a website and the interaction with the participants was based on e-mail which is a feasible method for delivering interventions to large numbers of people with OA. A future development could be to provide a mobile application for more efficient and automated delivery of intervention components. The use of the e-mail system to deliver a weekly website-link to the exercise program and provide an individually tailored behaviour change message was time consuming for the project associate. Digitally automated exercise programs and messages [31] could be utilised in the future for even more efficient delivery.

Table 1 Characteristics of patients with hip and/or knee osteoarthritis who attended baseline assessments ($n = 30$)

Demographics	
Age, years, mean (SD)	63.3 (9.5)
Female, *n* (%)	21 (70.0)
Body mass index, kg/m^2, mean (SD)	30.4 (6.7)
Living arrangement, living alone, *n* (%) [a]	11 (38)
Education level, ≥ 1 year of college/university, *n* (%)	19 (63)
Non-smokers, *n* (%)	29 (97)
Working full time, *n* (%)	13 (43)
Clinical characteristics	
Pain (NRS, 0–10, 0 = no pain), median (IQR)	5.0 (3.0, 6.3)
Disease activity (NRS, 0–10, 0 = no disease activity), median (IQR)	5.0 (3.8, 7.0)
Most troublesome joint, *n* (%)	
Knee (right or left)	26 (87)
Hip (right or left)	4 (13)
Total number of troublesome joints (range 0–9), *n* (%)	
1 to 4 joints	25 (83)
5–9 joints	5 (17)
Number of co-morbid conditions (range 0–15), *n* (%)[b]	
No co-morbid conditions	10 (33)
One co-morbid condition	14 (47)
2 to 4 co-morbid conditions	6 (20)

[a] $n = 29$ due to missing data

[b] Data based on the question: Is your health currently affected by one or more of these medical problems (each answered by yes/no): high blood pressure, angina/infarction/other cardiac disease, asthma/bronchitis/other pulmonary disease, allergy/rhinitis/eczema/, sciatica, cerebral haemorrhage/cerebral stroke, cancer disease, neurological disease (in brain- or nerve tissue), diabetes, metabolic disease, mental/psychological disease, kidney disease, liver disease, ulcer or other stomach disease, anaemia or other blood disease

Table 2 Logistics of the AktiWeb study in patients with hip and/or knee osteoarthritis

Logistics	**Outcome**
Enrolled	
Proportion of eligible patients enrolled	71% (35/49)
Assessment	
Proportion of patients providing valid accelerometer data at baseline assessment	86% (30/35)
Proportion of patients completing maximal cardiorespiratory exercise test according to protocol at baseline assessment	51% (18/35)
Proportion of patients returning exercise diary	77% (27/35)
Received exercise diaries per patient (0–12), median (range)	11 (1–12)
Proportion of enrolled patients providing data at 12-week follow-up assessments	63% (22/35)
Intervention delivery	
Time resources used on delivery of exercise programs and motivational messages, minutes per week/patient, mean (SD)	7.3 (1.1)
Time resources used by peer-supporters, minutes per week/patient	0[a]

[a] The peer-supporters were not contacted

Social support and peer encouragement are known to be important factors for exercise adherence [13, 14, 17]. However, the assigned peer-supporters were not utilised by patients in the present study. A possible reason may be that the behaviour change messages may have reduced the need for additional support during the 12-week program as similar messages have previously been shown to support adherence to home-base exercise in knee OA [49]. Qualitative research could establish the reasons why peer-supporters were not contacted by patients, and whether peer-support could be provided based on the patients' needs.

The motivational messages used in this study were developed specifically for patients with hip or knee OA,

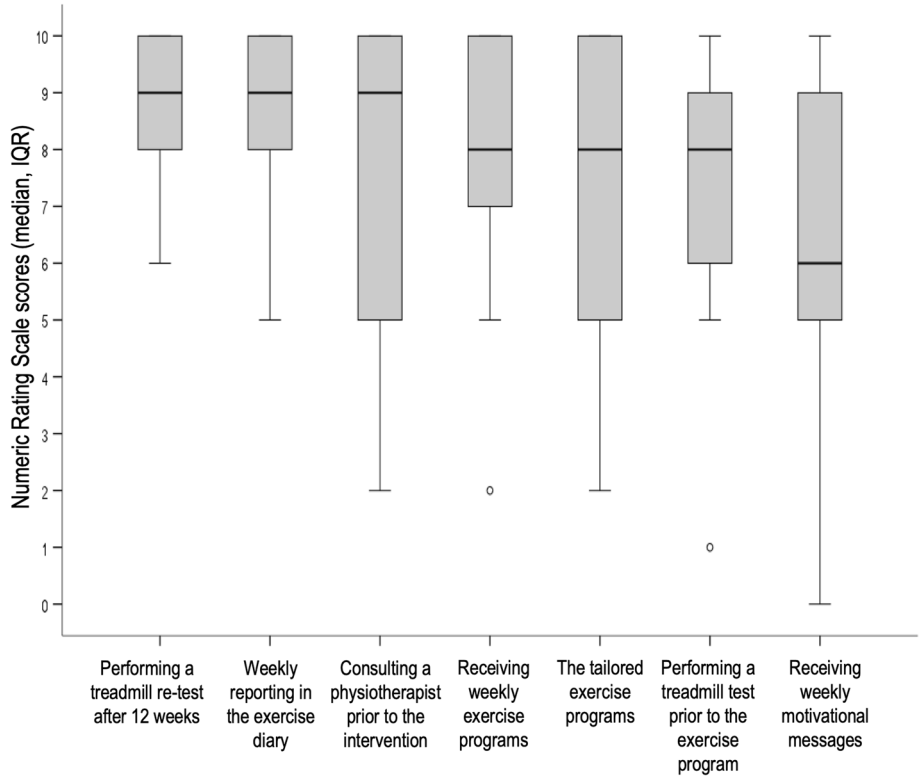

Fig. 3 The degree to which study components motivated patients to adhere to the exercise program ($n = 22$)

based on behaviour change techniques linked to barriers and facilitators of exercise adherence in this patient group [14, 31]. The messages, delivered via SMS, have been evaluated in a clinical trial in 110 people with knee OA, showing that adherence to a resistance exercise program was higher in the group that received the messages by SMS compared to the control group who did not receive messages [49]. Combined with a web-based self-directed exercise program, the SMS messages have also been shown to improve pain and function at 24 weeks in people with knee OA [50]. In the current study, most participants reported that the messages to some degree motivated them to adhere to exercise, but other interventional components (i.e. receiving weekly exercise programs and reporting in an exercise diary) were rated as even more important motivational factors. Collectively, these results show that methods for motivation and follow-up are appreciated by people with OA and should be used to enhance patients' adherence to exercise.

PA and exercise are important core treatments to maintain or improve functional capacity and cardiorespiratory fitness [3, 5]. In this study, a subset of the participants improved PA and cardiorespiratory fitness (VO_{2peak}) equal to the results reported in a recent meta-analysis including studies on patients with knee OA who followed aerobic exercise [51]. Even if the number of participants in our study was limited due to the COVID-19 pandemic, the positive results were supported also in the self-reported measures of pain and function. Thus, it seems that patients with lower limb OA can follow aerobic exercise programs outside of healthcare settings, and obtain improvement in physical fitness. However, with the uncontrolled nature of our feasibility study we cannot conclusively attribute changes in clinical outcomes to our intervention. Future robust randomised controlled trials are needed to definitively determine treatment efficacy.

Objective, valid testing of physical capacity is needed when providing individually tailored exercise programs to patients and is valuable to inform goal setting and to monitor adherence to prescribed exercise [3, 23]. In this study, accelerometery was used to evaluate patients' level of PA and a treadmill exercise test was used to measure fitness in a subgroup of the patients, and both were considered acceptable. Although all patients who attended baseline assessments provided valid baseline data for PA in our study, others have reported 10-28% missing at follow-up among individuals with OA (i.e. due to non-valid wear time or technical issues with the accelerometer) [52, 53]. Additionally, 31% of the participants had to perform a submaximal exercise test for assessment of fitness level.

Table 3 Outcome measures and proportions of patients with meaningful change or no change

	N	Baseline Mean (SD)	Follow-up Mean (SD)	Mean change (95% CI)	Proportion improved	Proportion no change	Proportion worsened
Physical activity							
Counts per minute/day	8	295.2 (70.7)	390.2 (110.8)	94.9 (45.0 to 144.8)			
MVPA minutes/day	8	33.2 (17.1)	49.6 (22.2)	16.4 (6.9 to 25.9)			
Cardiorespiratory fitness, VO_{2peak} (ml/kg/min)	8	25.05 (5.93)	26.88 (6.79)	1.83 (0.29 to 3.36)			
HOOS/KOOS, normalised scores (0–100, 100 = best score)							
Symptoms	21	46.0 (17.0)	55.3 (17.1)	9.3 (4.6 to 14.0)	48%	48%	5%
Pain	20	55.1 (19.5)	61.5 (20.2)	6.4 (1.5 to 11.3)	40%	55%	5%
ADL	21	62.7 (18.7)	71.8 (19.2)	9.1 (5.3 to 13.0)	52%	43%	5%
Sports/Rec	20	35.3 (26.1)	40.3 (29.1)	5.0 (− 2.4 to 12.3)	30%	45%	25%
QoL	21	34.7 (13.6)	42.7 (17.8)	8.0 (1.8 to 14.3)	43%	43%	14%
Numeric Rating Scales (NRS), 0–10, 0 = no pain							
NRS pain, last week	20	5.2 (2.2)	4.5 (2.4)	0.7 (− 0.1 to 1.4)	30%	60%	10%
NRS fatigue, last week	22	3.8 (3.1)	3.1 (2.7)	0.6 (− 0.5 to 1.8)	45%	41%	14%
NRS disease activity, last week	22	5.4 (2.1)	4.5 (2.1)	0.9 (− 0.1 to 1.9)	41%	41%	18%
Health-related quality of life							
EQ-5D-5L utility score (− 0.59 to 1)	16	0.79 (0.14)	0.85 (0.11)	0.06 (0.03 to 0.09)	38%	56%	6%
EQ-5D VAS (0–100, 100 = best health)	17	61.9 (15.1)	70.5 (18.3)	8.6 (1.2 to 16.0)	47%	41%	12%
Arthritis Self-Efficacy Scale							
Pain, mean (0–100)	20	57.4 (13.6)	56.5 (12.2)	0.9 (− 7.4 to 9.1)	30%	50%	20%
Symptoms, mean (0–100)	21	54.6 (10.9)	58.1 (-14.6)	− 3.5 (− 9.0 to 2.0)	38%	48%	14%
Exercise beliefs							
Self-efficacy, sum score (4–20)	21	14.8 (2.4)	16.8 (2.3)	− 2.0 (− 3.5 to − 0.4)	48%	43%	10%
Barriers to exercise, sum score (3–15)	20	11.7 (2.1)	11.8 (2.1)	− 0.1 (− 0.9 to 0.7)	25%	55%	20%
Benefits of exercise, sum score (5–25)	21	20.0 (3.2)	20.7 (2.5)	− 0.8 (− 0.2 to 0.5)	30%	55%	15%
Impact of exercise on arthritis, sum score (8–40)	21	31.9 (4.6)	33.2 (4.5)	− 1.3 (− 2.7 to 0.1)	24%	76%	0%

SD standard deviation, *95% CI* 95% confidence interval, *MVPA* moderate to vigorous physical activity, *VO2peak* peak oxygen uptake, *HOOS* Hip disability and Osteoarthritis Outcome Score, *KOOS* Knee injury and Osteoarthritis Outcome score, *ADL* function in daily living, *Sport/Rec* function in sport and recreation, *QoL* hip/knee-related quality of life

Thus, for use in large patient groups, simpler methods such as non-exercise-based fitness calculators [3] or easily conducted performance-based measures (i.e. 6-min walk test) [54] could be used to achieve the purpose of testing.

In this study, the exercise dosage was individually adjusted by a project associate based on the weekly digital exercise diaries in which adherence to prescribed exercise was reported. Self-reporting adherence to exercise may function as self-monitoring, which is recognised as an important facilitator for exercise adherence [14, 29]. As a further development to enhance the advantages of self-monitoring, the data from exercise diaries could be combined with data on self-reported OA symptoms [55]. Graphical illustrations could be produced to visualise the association between exercise and disease burden, which would be a useful tool for patients in optimising their dosage of PA.

The main limitation of this study is that restrictions due to the COVID-19 pandemic stopped the inclusion and limited the follow-up assessment of patients. Further, before recruitment the participants were pre-screened and selected from a cohort of patients referred to specialised healthcare for surgical consultation, and the results may therefore not be generalisable to the total OA population. Another limitation is that we did not predefine criteria to determine whether to stop or proceed with a future larger trial. However, we have made a thorough discussion of results to inform a possible future RCT. Even if strict exclusion criteria for high intensity exercise testing was applied, only one patient was excluded due to this. Thus, following the ACSM guidelines [23] for high intensity testing should be done in future trials.

Conclusion

A web-based exercise program with a stepwise, progressive design delivered by a patient organisation was found to be feasible, acceptable and safe in patients with hip and knee OA, and positive results were found for PA, cardiorespiratory fitness and several

patient-reported outcomes. The findings in this feasibility study can inform future trials as our promising results support that patient organisations can play the role as a valuable resource in long-term follow-up of patients with chronic conditions, and thereby potentially alleviate the healthcare system.

Abbreviations
BORG RPE: BORG Rating of Perceived Exertion; CPM: Counts per minute; EQ-5D VAS: EQ-5D Visual Analogue Scale; HOOS: Hip disability and Osteoarthritis Outcome Score; KOOS: Knee injury and Osteoarthritis Outcome score; MVPA: Moderate to Vigorous Physical Activity; NRF: Norwegian League against Rheumatism; NRS: Numeric Rating Scale; OA: Osteoarthritis; PA: Physical activity; REK: Regional Committee for Medical and Health Research Ethics; SD: Standard deviation; SUS: System usability scale; VO_{2peak}: Peak oxygen uptake; CI: Confidence interval.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40814-022-01110-3.

Additional file 1. The exercise program.

Acknowledgements
The authors wish to acknowledge and express gratitude to all patients for participating, Knut Øderud (Norwegian League against Rheumatism patient representative) who gave invaluable input on the exercise program and website components, Sissel Syvertsen and Ågot Hamre for volunteering to be peer-supporters and Anne Christie who contributed in the study conception and data collection.

Authors' contributions
All authors (KLJ, HD, KBH, KN, CF, OMW, RSH, RKN, KLB, ATT) were involved in conception of the study, and contributed to the study design, critical revision and final approval of the submitted manuscript. KLJ, HD, KN, CF and ATT contributed in data collection, and KLJ, HD, KBH and ATT were responsible for data analyses and interpretation. All authors read and approved the final manuscript.

Funding
The project was funded by Dam foundation (2019/FO247595) through the Norwegian League against Rheumatism. The funding agency was not involved in any study processes (planning, design, data collection, analysis, interpretation of data, writing and submission of the manuscript) in this study. RSH is supported by a National Health & Medical Research Council Senior Research Fellowship (#1154217). KLB is supported by a National Health & Medical Research Council Investigator Grant (#1174431).

Availability of data and materials
The datasets generated and analysed during the current study are not publicly available because the data include identifiable data on individuals. De-identified data may be made available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was carried out in compliance with the Declaration of Helsinki and was evaluated and approved by the Regional Committee for Medical and Health Research Ethics (REK south-east, 2018/2198) and approved by a Data Protection Officer at Diakonhjemmet Hospital (reg.no. 00138). All patients received verbal and written information about the study and provided written informed consent.

Consent for publication
N/A.

Competing interests
The authors declare that they have no competing interests.

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Received: 25 May 2021 Accepted: 5 July 2022
Published online: 20 July 2022

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Publisher's Note

Paper IV

IV. Joseph KL, Dagfinrud H, Hagen KB, Nordén KR, Fongen C, Wold OM, Hinman RS, Nelligan RK, Bennell KL, Tveter AT. Adherence to a web-based exercise program – a pre-post study among patients with hip or knee OA. *Submitted* to Journal of Rehabilitation Medicine, January 2023.

Adherence to a web-based exercise program – a pre-post study among patients with hip or knee OA

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Abstract

Objective

To explore adherence to a 12-week web-based aerobic exercise program and map barriers for completing exercise sessions in patients with hip or knee OA.

Design: Single-arm pre-post study

Subjects: Patients with hip or knee OA in specialist healthcare, 40-80 years and not candidates for joint surgery.

Methods: Adherence to a 12-week exercise program was reported in an electronic diary and defined as having completed ≥2 exercise sessions a week for at least 8 weeks. Baseline differences between adherent- and non-adherent groups in demographics, symptoms and disability, cardiorespiratory fitness, and physical activity were assessed using Mann-Whitney U or Chi-square tests. Reasons for not completing exercise sessions were reported in a weekly diary.

Results: Thirty patients (mean age 62.5 years, 74% female) were included. Median baseline pain (NRS 0-10) was 5. Fifteen patients (50%) were categorized as adherent and 15 (50%) non-adherents. At baseline, non-adherent patients were less active (p=0.015) and had lower cardiorespiratory fitness (p=0.041). The most frequently reported exercise barrier was sickness. Less than 10% reported OA-related pain as a barrier.

Conclusion: Half of the hip or knee OA patients adhered to the digitally delivered exercise program and most patients experienced sickness as a barrier for adherence to exercise.

Trial registration: ClinicalTrials.gov, NCT04084834. The Regional Committee for Medical and Health Research Ethics South-East, 2018/2198.

Keywords (3-10 words)

Exercise; Adherence; Osteoarthritis; Management; Web-based; Barriers; Motivation; Digital technology

Introduction

Exercise is recognized as an important part of the treatment plan for a wide range of chronic diseases, for curbing symptoms as well as for reducing comorbidities (1). For musculoskeletal diseases like osteoarthritis (OA), numerous studies have shown beneficial effects of supervised exercise, and adherence to prescribed exercise is associated with reduced joint pain, improved physical function and better health-related quality of life (2-4).

Evidence supports exercise as a core component in the management of people with OA (5), and adherence to regular exercise is crucial. Long-term adherence to a prescribed exercise program depends on a range of factors influencing motivation, capability, and opportunity for participating in exercise (6). Barriers to exercise, like pain, functional limitation and poor exercise beliefs, can be overcome by instruction, advice, encouragement, feedback, and support from health care providers (7). A challenge is, however, that the need for long-term individual supervision and support for this large and increasing patient group cannot be met solely within the healthcare system. Development of alternative delivery and follow-up methods is therefore required, and digital technologies (i.e. phone-, SMS-, app- or web-based) for delivery of self-management and exercise programs may represent a more sustainable way to support patients with life-long need for management (8).

Regular adherence to exercise is important for gaining and maintaining positive health effects and is therefore a prerequisite for considering "exercise as medicine" (4). Web-based exercise programs may be a sustainable tool in long-term management of people with OA, but more insight is needed into how patients adhere to such programs. Hence, the aim of this study was to explore the adherence to a 12-week, web-based aerobic exercise program and map the reasons for not completing exercise sessions in patients with hip or knee OA.

Methods

Design and participants:

This was a pre-post, single-arm intervention study addressing adherence to a web-based aerobic exercise program for patients with OA. The exercise program and methods of delivery are described in detail elsewhere (9). In short, patients aged 40-80 years, referred to Diakonhjemmet Hospital Norway for surgical consultation due to hip or knee OA, were eligible if not considered candidates for surgery. Exclusion criteria were inability to

understand or write Norwegian, to walk unaided and continuously for 15 minutes, any absolute or relative contradictions to maximal exercise testing and inability to access the internet. Forty-nine patients were identified and received verbal and written information about the study and 35 were ultimately enrolled into the study.

Data collection and intervention:

Patients who consented to participate were asked to complete an electronic baseline questionnaire including demographics (age, gender, body mass index (BMI), education, employment status, living alone/together with someone, smoking, comorbidity), OA-related symptoms and disability (troublesome joints, 'Hip disability and Osteoarthritis Outcome Score' (HOOS) or 'Knee injury and Osteoarthritis Outcome Score' (KOOS) (0-100, 100= no disability) (www.koos.nu), and pain (numeric rating scale (NRS) 0-10, 0=no pain). Physical activity (moderate to vigorous, min/day) was measured by a hip-worn accelerometer (ActiGraph GT3X+, Pensacola, FL), which the patients were asked to wear for seven consecutive days. Additionally, baseline assessments included a maximal (n=20) or submaximal (n=9) cardiorespiratory fitness test ($VO_{2peak/max}$), and questions about physical activity habits and pain during physical activity, which was used to determine each patient's initial exercise level (described in detail elsewhere (9)).

The 12-week web-based program was developed in close collaboration with a patient organization (the Norwegian Rheumatic Association) and was designed as a progressive aerobic exercise program. The program comprised three aerobic sessions per week (two interval sessions and one light to moderate intensity session) across five different exercise levels. For each increment in exercise level, the weekly exercise dosage (duration and/or intensity using the Borg Rating of Perceived Exertion (10) ranging from 6 (no exertion) to 20 (maximal exertion) as guidance) was increased. The detailed program is published elsewhere (9). The exercise level for the subsequent week was determined by the project manager based on the number of sessions completed and the possible predefined reasons for not completing the exercise program (one or more barriers selected from a predefined list (11) reported by the individual patient in an electronic exercise diary). If the patient reported to have completed all three exercise sessions, the exercise level was increased every other week until the highest level was reached. If all exercise sessions were not completed, the same exercise level was kept for the subsequent week. The exercise program was e-mailed to the patients at the beginning of each week by the project manager together with contact information to peer

supporters and a tailored message addressing any exercise barriers reported in the exercise diary. An additional facilitator message designed to encourage weekly exercise adherence (11) was e-mailed to the patient in the middle of the week. After 12 weeks, the patients answered an electronic follow-up questionnaire, and their cardiorespiratory fitness and physical activity level were reassessed.

Adherence

Adherence to the exercise sessions was collected through the weekly electronic exercise diary, including the patients' reporting of completed exercise sessions and the intensity for each session using the Borg Scale. Adherence to the 12-week exercise program was defined as having completed ≥2 exercise sessions a week (according to the prescribed Borg intensity) for at least 8 weeks (12). Patients not submitting any exercise diaries were categorized as non-adherent.

Barriers to adherence

Patients who completed ≤2 of the prescribed sessions in each week were asked to select one or more reasons for not completing all three exercise sessions. The predefined reasons ('forgot', 'too tired', 'joint pain', 'worried exercise is causing pain/injury', 'exercise do not help', 'boring', 'lack of time', 'life stress') are common barriers identified for patients with OA, and conform with a theory-supported behaviour change program for people with OA (11). An additional 'none of the alternatives apply to me' with a free-text option was added.

Statistics

Data are presented as median and interquartile range (IQR, 25th and 75th percentile) or frequencies and percentage. Patients adhering (adherent group) or not adhering (non-adherent group) to the exercise program are shown graphically. Mann-Whitney U test or Chi-square were used to examine differences between the adherent and non-adherent groups in baseline demographics, OA-related symptoms and disability, self-efficacy, cardiorespiratory fitness, and physical activity level. Mapping of barriers are shown graphically. Significance level was set to $p<0.05$. IBM SPSS Statistics version 27 was used for statistical analyses.

Results

In total, 30 patients were included in the analyses. After the 12-week intervention, 15 patients (50%) were categorized as adhering to the exercise program and 15 (50%) were categorized as not adhering to the program (Figure 1). Due to the Covid-19 pandemic, four patients had to

discontinue the program: two ended at 10 weeks but fulfilled the adherence criteria and were placed in the adherent group, and two did not fulfill the criteria and were placed in the non-adherent group.

Baseline characteristics are shown in Table 1. The median age of the cohort was 64 years, the majority (74%) were female and most (85%) had BMI ≥25 kg/m^2. The patients reported moderate pain level (the last week) with a median NRS score of 5. The adherent- and non-adherent groups were similar at baseline with the exception that more patients in the non-adherent group reported living alone (p=0.019), and that patients in the adherent-group were more active (p=0.015) and had better cardiorespiratory fitness (p=0.041) (Table 2).

Regarding barriers, the 'none of the alternatives applies to me'-option was most often selected. Among the free-text answers, sickness was most frequently reported and less than 10% of the reported barriers were related to OA joint pain (Figure 2).

Discussion

In this study, half of the patients adhered to the digitally-delivered aerobic exercise program. The intervention was delivered during the Covid-19 pandemic, inducing some situation specific barriers for many patients, but still, the results show that half of OA-patients referred for surgical consultation can follow a web-based exercise program. Patients who were adherent were significantly more physically active and had better cardiorespiratory fitness at baseline than the non-adherent group. Less than 10% of the participants reported OA-related pain as a barrier for adherence to exercise.

Adhering to exercise over time is of vital importance for patients with OA, as an action to reduce disease symptoms as well as to reduce risk of comorbidity. Measuring adherence is, however, complex, and comparison of adherence rates between studies is difficult due to lack of standardization of measuring methods and inconsistency of definitions and registration of adherence (13). Self-reporting in diaries is a common method for reporting adherence, and by use of weekly reporting in the current study, we found the adherence rate to be comparable to the results of an 8-week physiotherapist-guided strengthening exercise study (14).

Despite the small number of participants in our study, our sample is reflective of those that are referred for surgical consultation in specialist healthcare due to hip or knee OA, and as such, they likely represent patients with severe joint disease in need of long-term follow-up.

The current intervention was carried out during the Covid-19 pandemic, but still, half of the patients adhered to the digitally-delivered program, indicating that this method can be regarded a sustainable follow-up alternative. If about half of the patients can follow a digitally delivered program, extra resources may be allocated to patients who are non-adherent. Based on the current study, people with poor physical fitness or reporting low physical activity may be more prone to be non-adherent.

Exercise is recommended as first-line treatment for patients with OA (5). For obtaining optimal health benefits from exercising ('exercise as medicine'), individual adoption of the program (including progression of the workload) and sufficient adherence to the program are needed. An advantage with web-based delivery is the possibility of e-mail automatically triggered by the lack of response, reminding people to submit their diary and pro-actively sending them a facilitator message. Patients at risk for dropping out can be identified, and automatically approached and motivated to continue exercising. Further, the patient-reported exercise diaries provide data on number of fulfilled exercise sessions, intensity and total workload, creating a basis for developing individual progression algorithms, ensuring correct dosage for optimal health benefit for the individual patient. Exploiting advantages of web-based delivery of treatment- and support programs must be part of the research agenda in the field of chronic diseases in the years to come.

Support to overcome barriers is an important aspect of facilitating uptake and adherence to exercise (7). However, the current study showed that our predefined barriers provided for reporting in the exercise diary had limited relevance for our sample of participants. This finding was supported in another study of OA patients (15), indicating that barriers to exercise are varied and diverse and that strategies to overcome barriers must be tailored to the individual in order to maximize success. The most common barrier reported in free-text in the current study was sickness, which may partly be explained by the ongoing Covid-19 pandemic.

This study has some limitations. The pre-post design and the absence of a control group do not allow for confirmative causal conclusions, and the modest sample size limits the generalizability of the results. Further, there is potential for misclassification of participants who didn't return diaries and were classified as non-adherent, as they may have exercised without submitting the diary. Direct comparison with other studies is difficult due to different programs and methods.

A strength of the study was that patients were consecutively recruited from those referred for surgical consultation, and the results and hypotheses are probably representative for this group of OA patients. Further, patient representatives were involved in the development of the program, which probably increased the relevance and suitability, which in turn may have influenced the adherence positively.

Conclusion

Half of the hip or knee OA patients adhered to the digitally-delivered exercise program, indicating that web-based exercise delivery can be valuable in supporting adherence to exercise programs for patients with hip or knee OA. Most patients experienced sickness as a barrier for adherence to exercise, and patients with low objective levels of physical activity and physical fitness may be at risk of non-adherence to web-based program delivery.

Conflict of interest and funding

The authors have no conflicts of interest to declare. The project was funded by foundation Dam (2019/FO247595). The funding agency was not involved in any study processes.

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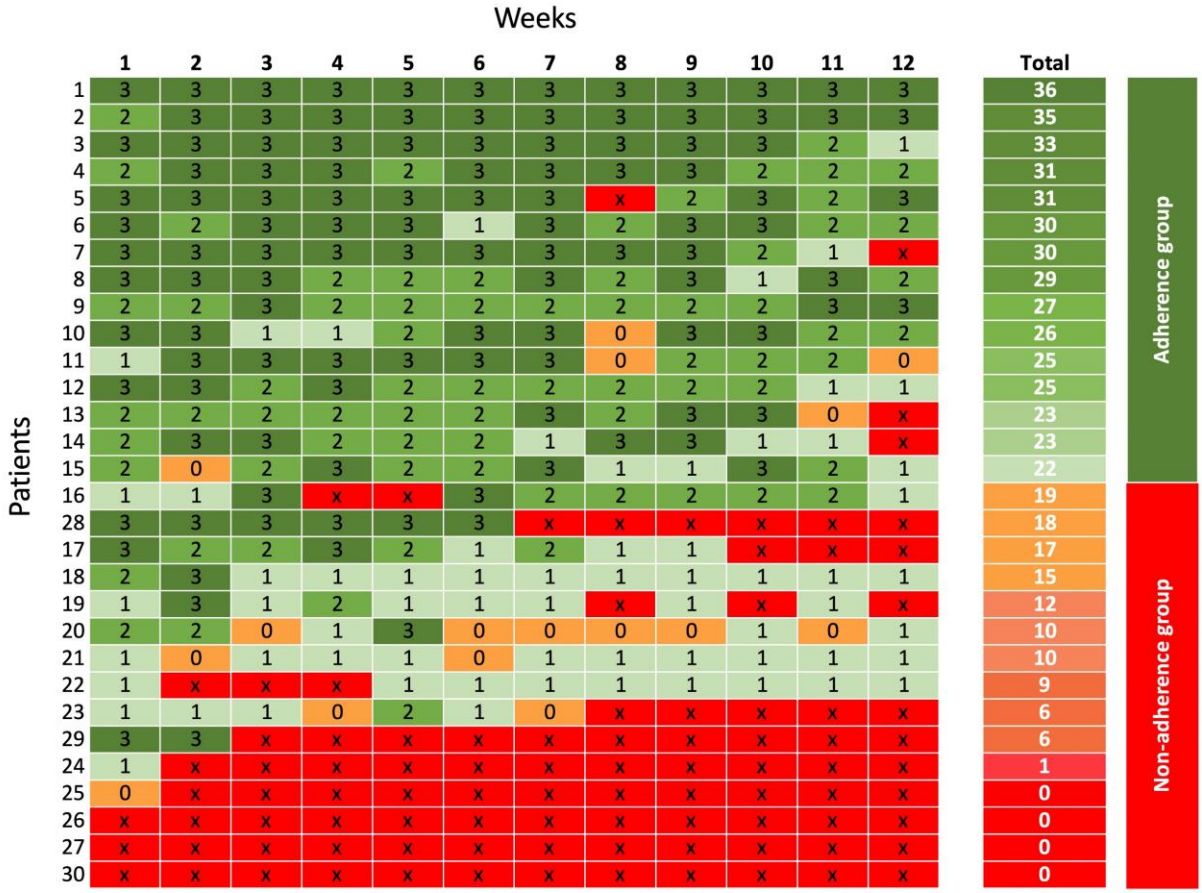

Figure 1. Individual patient adherence/non-adherence profiles, where the number in the cell refers to the number of exercise sessions completed each week (and in total), and the x indicates that the exercise diary was not submitted (=categorized as no exercise sessions completed).

Table 1 Baseline characteristics for patients with hip or knee OA shown for the total group and by exercise adherent- and non-adherent group with p-values for the difference between the groups.

	All (n=30)	Adherence group (n=15)	Non-adherence group (n=15)	p-value
Age (years), median (iqr)	64 (56- 70)	63 (51 - 67)	67 (58 - 72)	0.25
Gender (female), n (%)	21 (70)	10 (67)	11 (73)	0.69
BMI (kg/m2), median (iqr)	28.3 (25.5 - 34.4)	28.0 (25.7 - 32.1)	28.7 (24.9 - 38.3)	0.68
Education (≥1 year of college/university), n (%)	19 (63)	9 (60)	10 (67)	0.70
Fulltime employment, n (%)	13 (43)	8 (53)	5 (33)	0.27
Living alone, n (%)	11 (37)	2 (13)	9 (60)	**0.011**
Non-smoker, n (%)	29 (97)	14 (93)	15 (100)	0.31
Proportion with comorbidity, n (%)	20 (67)	9 (60)	11 (73)	0.44
OA-related symptoms				
Most troublesome joint, n (%)				
Hip (right/left)	4 (13)	2 (13)	2 (13)	1.00
Knee (right/left)	26 (87)	13 (87)	13 (87)	
Proportion with additional troublesome joint (hip/knee/ankle/hand), n (%)	24 (80)	13 (87)	11 (73)	0.36
Proportion using daily pain medication, n (%)	12 (40)	6 (40)	6 (40)	1.00
Pain last week (NRS 0-10, 0=no pain)	5 (3 - 6)	5 (3 - 6)	4 (3 - 7)	0.57
Disease activity last week (NRS 0-10, 0=no disease activity)	5 (4 - 7)	5 (4 - 7)	4 (3 - 7)	0.33
Fatigue last week (NRS 0-10, 0=no fatigue)	2 (0 - 6)	3 (0 - 7)	2 (0 - 5)	0.44
Hip/knee OA symptoms and disability (HOOS/KOOS)				
Symptoms (0-100, 100= no disability)	46 (36 - 59)	46 (39 - 64)	43 (36 - 57)	0.57
Pain (0-100, 100= no disability)	58 (44 - 71)	58 (44 - 72)	54 (43 -67)	0.65
Function in daily living (0-100, 100= no disability)	65 (56 - 75)	63 (61 - 74)	72 (39 - 82)	0.90
Function in sport and recreation (0-100, 100= no disability)	25 (13 - 50)	35 (17 - 50)	25 (10 - 50)	0.46
Hip/knee related quality of life (0-100, 100= no disability)	41 (30 - 45)	31 (25 - 44)	44 (31 -50)	0.39
Moderate to vigorous physical activity (min/day), median (iqr)	27 (12 - 39)	31 (25 - 46)	19 (3 - 28)	**0.033**
Cardiorespiratory fitness ($VO_{2peak/max}$), median (iqr)	28.7 (22.9 - 31.2)	29.3 (26.0 - 33.2)	23.7 (20.2 – 30.8)	**0.029**

P-values analysed by Mann-Whitney U test or Chi-square. BMI, Body Mass Index; NRS, Numeric Rating Scale; HOOS, Hip disability and Osteoarthritis Outcome Score, KOOS, Knee injury and Osteoarthritis Outcome score; $VO_{2peak/max}$, Peak/max Oxygen Uptake.

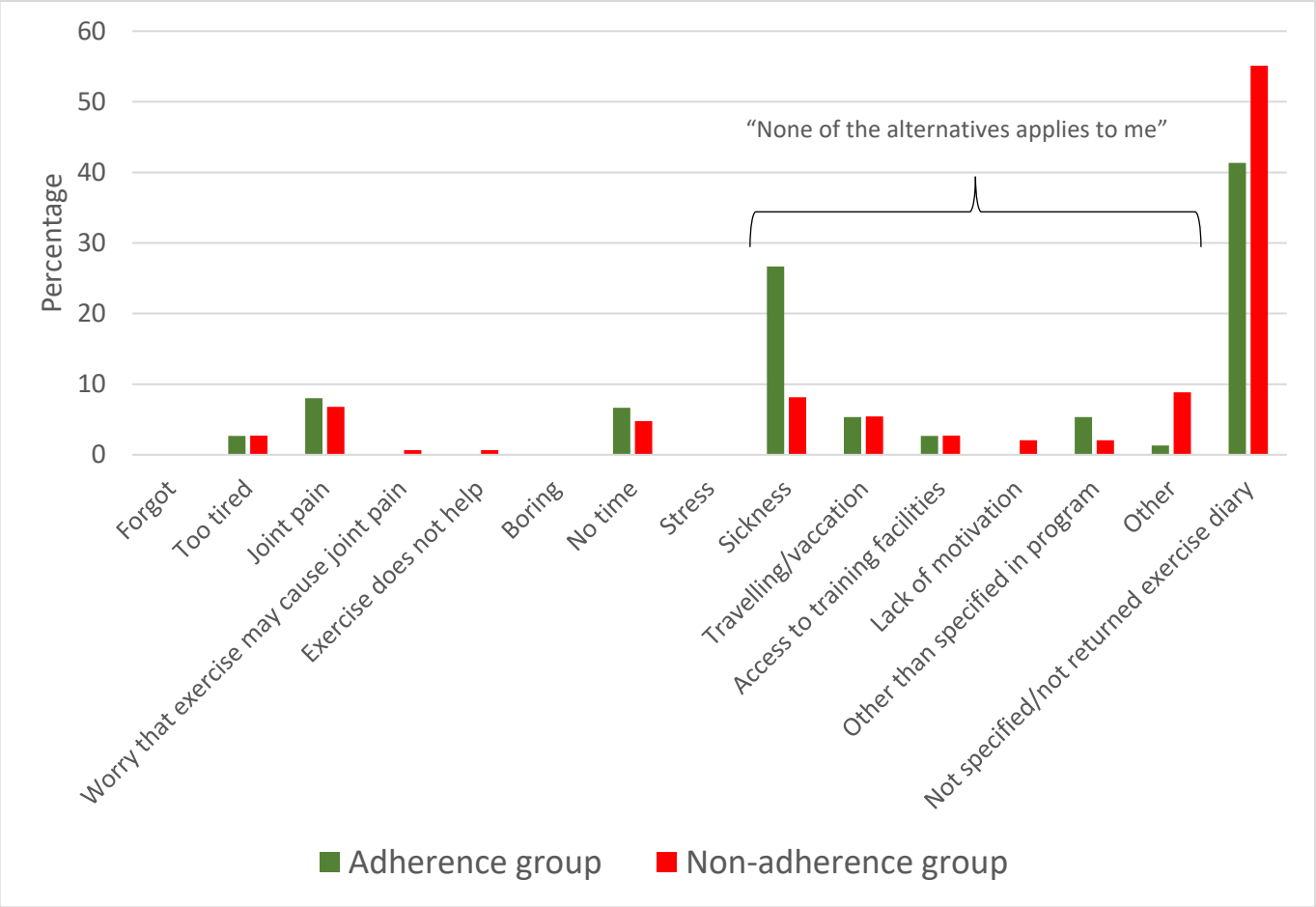

Figure 2. Barriers reported for not completing ≥3 exercise session/week, shown in percentages by exercise adherence- and non-adherence group.