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COST-EFFECTIVENESS OF AN 8-WEEK SUPERVISED EDUCATION AND EXERCISE THERAPY PROGRAM FOR KNEE AND HIP OSTEOARTHRITIS: A PRE-POST ANALYSIS OF 16,255 PATIENTS PARTICIPATING IN GOOD LIFE WITH OSTEOARTHRITIS IN DENMARK (GLA:D®)

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Complete List of Authors:	Grønne, Dorte; University of Southern Denmark, Department of Sports Science and Clinical Biomechanics Roos, Ewa; University of Southern Denmark, Department of Sports Science and Clinical Biomechanics Ibsen, Rikke; I2minds Kjellberg, Jakob; VIVE - The Danish Center for Social Science Research Skou, Søren; University of Southern Denmark, Department of Sports Science and Clinical Biomechanics; Occupational Therapy Næstved-Slagelse-Ringsted Hospitals, Department of Sports Science and Clinical Biomechanics
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COST-EFFECTIVENESS OF AN 8-WEEK SUPERVISED EDUCATION AND EXERCISE THERAPY PROGRAM FOR KNEE AND HIP OSTEOARTHRITIS: A PRE-POST ANALYSIS OF 16,255 PATIENTS PARTICIPATING IN GOOD LIFE WITH OSTEOARTHRITIS IN DENMARK (GLA:D®)

Dorte T. Grønne[1] PT, MSc, Ewa M. Roos[1] PT, PhD, Rikke Ibsen[2] MSc, Jakob Kjellberg[3] PhD, Søren T. Skou[1,4] PT, PhD

[1] Research Unit for Musculoskeletal Function and Physiotherapy, Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, Denmark

[2] I2minds, Aarhus, Denmark

[3] VIVE - The Danish Center for Social Science Research, Copenhagen, Hovedstaden, Denmark

[4] Department of Physiotherapy and Occupational Therapy, Næstved-Slagelse-Ringsted Hospitals, Denmark

Emails:

DTG: dgronne@health.sdu.dk; EMR: eroos@health.sdu.dk ; RI: rikke@i2minds.dk; JK: jakj@vive.dk; STS: stskou@health.sdu.dk

Corresponding author:

Dorte Thalund Grønne; IOB, SDU, Campusvej 55; DK-5230 Odense M; email: dgronne@health.sdu.dk; Telephone: +45 40 77 99 39

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ABSTRACT

Objectives: To evaluate one-year cost-effectiveness of an 8-week supervised education and exercise therapy program delivered in primary care to patients with symptomatic knee or hip osteoarthritis (OA).

Design: A register-based pre-post study linking patient level data from the Good Life with osteoArthritis in Denmark (GLA:D®) registry to national registries in Denmark.

Setting and participants: 16,255 patients with symptomatic knee or hip OA attending GLA:D®.

Intervention: GLA:D® is a structured supervised patient education and exercise therapy program delivered by certified physiotherapists and implemented nationwide in Denmark.

Outcome measures: Raw and adjusted health care costs per Quality-Adjusted Life Year (QALY) gained in a one-year horizon calculated as the ratio of change in health care costs to change in EuroQoL 5-Dimensions 5-Level questionnaire (EQ-5D). Adjusted measures were estimated using a generalized estimating equation gamma regression model for repeated measures. Missing data on EQ-5D were imputed with Multiple Imputations (3 months: 23%; 1 year: 39 %). A sub-analysis repeating all analyses in patients with high compliance was conducted.

Results: Adjusted change in health care cost was 298€ (95% CI: 206-419)/640€ (400-1,009) and change in EQ-5D was 0.035 (0.033-0.037)/0.028 (0.025-0.032) for knee and hip patients respectively. Hence estimated adjusted health care costs per QALY gained was 8,497€ (6,242-11,324) for knee and 22,568€ (16,000-31,531) for hip patients. Restricting the regression analysis to patients with high compliance, the adjusted health care costs per QALY gained decreased to 5,438€ (2,758-9,231) for knee and 17,330€ (10,041-29,364) for hip patients primarily due to lower change

in costs. Health care costs per QALY were below conventional thresholds for willingness-to-pay at 22,804€ (20,000£) and 43,979€ (50,000 USD).

Conclusions: A structured 8-week supervised education and exercise therapy program delivered in primary care was cost-effective at one year in patients with knee or hip OA supporting large scale implementation in clinical practice.

Keywords: knee, hip, osteoarthritis, exercise therapy, patient education, cost-effectiveness

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The study included a large number of rural and urban patients with knee or hip OA treated in primary care across Denmark.
- All costs reported are real-life costs retrieved on an individual level from a range of high-quality national registries.
- The study is a pre-post study reporting change in health care costs against change in generic health related quality of life (EQ-5D).
- Health care costs per Quality-Adjusted Life Year (QALY) was reported in a one-year horizon and additional change in health care costs were reported in a three-year horizon.
- 23% and 39 % of the patients did not provide data on EQ-5D immediately following the intervention and at one year respectively, and the missing data was imputed with Multiple Imputations.

INTRODUCTION

Knee and hip osteoarthritis (OA) are major contributors to disability and chronic pain worldwide and the implications for both the patients and health care systems are severe,[1,2]. The cost related to OA is estimated to be between 1% and 2.5% of a country's gross domestic product (GDP) in high-income countries,[1], and total annual costs in Europe are estimated to be up to 817 billion € (2013),[3]. The number of people living with OA has increased over the last years and is expected to increase substantially in the future due to an ageing and more overweight and obese population,[4]. This will have extensive societal impact, emphasizing the need for identifying and implementing cost-effective treatment options that can help relieve the pressure health care services around the world are facing,[4].

Clinical guidelines recommend a stepwise treatment approach, including education and exercise therapy as first-line treatment for knee and hip OA,[5-8] with substantial evidence supporting the effects of supervised exercise therapy on pain and physical function,[9-10]. However, studies of quality of care report that exercise therapy is underutilized, estimated to be provided to less than 40% of patients with OA,[11,12]. To support the implementation of clinical guidelines into clinical practice, Good Life with osteoArthritis in Denmark (GLA:D®) was initiated in 2013 and has been implemented across Denmark. The treatment part of GLA:D® is an 8-week supervised patient education and exercise therapy program delivered in primary care for patients with knee or hip OA and has shown positive results on pain, physical function, quality of life (QOL), intake of painkillers and sick leave,[13].

Results from previous evaluations of the cost-effectiveness of first-line treatment including exercise therapy and targeting knee or hip OA are heterogeneous, and little is known about the cost-effectiveness of supervised education and exercise therapy implemented in primary care,[14,15]. Such evaluation is warranted when deciding whether to implement a structured first-line treatment program, and therefore the aim of the study was to evaluate the cost-effectiveness of GLA:D®. We hypothesized that GLA:D® would be cost-effective for both knee and hip OA patients.

METHOD

Study Design

This is a register-based pre-post study evaluating the cost-effectiveness of an 8-week supervised education and exercise therapy program (GLA:D®) for patients with symptomatic knee or hip OA by linking patient level data from the GLA:D® registry to national registries in Denmark. We reported mean actual health care costs and costs to home care and public transfer payments in a three-year horizon and reported health care costs per QALY gained in a one-year horizon calculated as the ratio of change in health care costs to change in QOL. The study conforms to the CHEERS statement for reporting health economic evaluations and recommendations for reporting cost-effectiveness analyses,[16,17].

Intervention

GLA:D® is a structured treatment program consisting of two patient education sessions, a session with an expert patient, when available, and of 12 one-hour sessions (delivered twice weekly) of supervised group-based neuromuscular exercise therapy,[18,19]. Treating therapists are physiotherapists certified to deliver the intervention on a 2-day course and patients are usually referred to the program by their general practitioner or an orthopaedic surgeon, but they may also refer themselves directly. From 2014 to 2016, the GLA:D® program was delivered in 283 private clinics across the country and in 28 municipal rehabilitation centers of 98 municipals in Denmark. Most of the patients attending the program in private physiotherapy clinics would receive public reimbursement of approximately 40% of the fee and most patients attending municipal rehabilitation centers would not be charged. A detailed description of the GLA:D® program has previously been published,[13].

The GLA:D® registry has previously been approved by the Danish Data Protection Agency (no. 10.084) and according to the local ethics committee of the North Denmark Region, ethics approval of GLA:D® was not needed. According to the Danish Data Protection Act, patient consent was not required as personal data was processed exclusively for research and statistical purposes.

Population

Patients are eligible for the GLA:D® program if they have a clinical diagnosis of knee and/or hip OA as evaluated by the treating physiotherapist i.e. pain or functional limitations associated with knee or hip OA and do not meet any of the following exclusion criteria: 1) another reason for the joint symptoms than OA (e.g. tumor, inflammatory joint disease or patellar tendinopathy), 2) other

symptoms that are more pronounced than the OA symptoms (e.g. chronic generalized pain or fibromyalgia), or 3) do not understand Danish. According to international,[20] and Danish,[21] guidelines radiographs are not needed for a clinical diagnosis of OA, and therefore not part of the GLA:D® eligibility criteria. The current study included patients enrolled between February 4, 2014, when collection of the EuroQoL 5-Dimensions 5-Level questionnaire (EQ-5D) was initiated, and December 31, 2016, allowing for one year follow up since information on all costs was available until the end of 2017. Patients with available baseline information on EQ-5D and information on whether a knee or a hip joint was the most affected joint were included in the study. Reporting mean costs in a three-year horizon was restricted to patients entering the program before December 31, 2014, allowing for three-year follow up, and reporting costs for public transfer payments were restricted to patients aged 18 to 63 years both in the pre- and post-intervention period to ensure that they did not turn 65 during the post-period which was the retirement age in Denmark in 2017. To cover living expenses public transfer payments are in Denmark provided to adults under the age of retirement who e.g. are unemployed, have low/no ability to work or are enrolled in education.

Variables

Data in the GLA:D® registry are collected at baseline, following the intervention (~3 months), and at 12 months and includes demographics, a mix of therapist and patient-reported health measures and outcome measures as well as compliance,[13]. Via the Civil Registration number (CPR), which identifies every citizen in Denmark, the GLA:D® registry was linked to national registries from where actual individual level utilization of somatic health care services (including use of primary health care services, secondary health care services, and use of preceptive medication; i.e. excluding

use of psychiatric health care services), home care, and public transfer payments were retrieved,[22]. In Denmark home care including practical help and personal care is offered to citizens with low functional level who are unable to manage everyday life on their own. All prices and costs were converted into Euros (€) and reported in present values (2017-level) based on the Danish Consumer Price Index. Costs were given as mean costs per month (one-year horizon) or year (three-year horizon) and public transfer payments were given as full-time weeks (37 h per week) per month (one-year horizon) or per year (three-year horizon).

Costs related to primary health care services, including visits to physiotherapist, chiropractor, general practitioner, and others (e.g. medical specialist, laboratory work, dentist), were obtained from the Danish National Health Insurance Service Registry. Within the primary health care sector in Denmark physiotherapy is delivered both in private clinics and in municipality settings however, costs for interventions delivered in municipal settings were not available and therefore not included in the analysis. Services and admissions related to secondary health care, including total somatic inpatient and outpatient services, were obtained from the Danish National Patient Registry and associated costs were estimated based on the Danish Case Mix System. The Danish National Patient Registry holds information on all inpatient admissions and outpatient activities, including accident and emergency visits in Danish hospitals. Every contact is coded in a classification system incorporating ICD-10 codes and use of resources in contacts where surgery in the knee or hip occurred were reported separately. Costs for prescriptive medications were obtained from the Danish National Prescription Registry holding information on all prescriptions on medications, including date of purchase, number of packages and the reimbursement paid by public funds. All drugs are classified according to the Anatomical Therapeutic Chemical Classification System (ATC) and painkillers (ATC-codes: N02A, N02B, M01A, M02AA) and other medications were reported separately. Information on number and duration of visits for personal care and practical

help, respectively, was retrieved from Statistics Denmark and the average care costs per hour (2017) in Denmark was used to calculate costs. Information on nursing care was not available and therefore not included in the analysis. Information on public transfer payments was retrieved from the Registry for Public Transfers, which holds information on type and hours of public transfer payments and was reported as the number of weeks receiving transfer payment (unemployment, sheltered employment, sick leave, rehabilitation, education, disability pension, early retirement).

Outcome was reported as QALYs gained measured with EQ-5D converted into an index score using time-trade-off based weights from the Danish crosswalk value set (-0.624 to 1; worst to best),[23]. The EQ-5D comprises of five dimensions: Mobility, self-care, usual activities, pain discomfort and anxiety/depression each having five levels of response options from 'no problems' to 'severe problems',[24]. QALYs combine time lived and QOL into a single index number where '1' corresponds to one year of full health and '0' corresponds to being dead.

Information on the covariates age (continuous), sex (male or female), marital status (married/coliving or single), ethnic background (western or not western), educational level (primary, secondary, vocational, short-term, bachelor, long-term or unknown) and administrative region (Capital, Zealand, Southern Denmark, Central Denmark or North Denmark) were retrieved from the Danish Civil Registration System. Most affected joint (knee or hip) and information on compliance were therapist-reported and high compliance was defined as patients attending at least 10 supervised exercise sessions. Type of clinic (private or municipal) was retrieved from the GLA:D® registry and whether the patient died during follow up was retrieved from the Danish Civil Registration System.

Statistical analyses

Descriptive statistics for baseline characteristics, average and predicted costs from somatic health care services and home care and average and predicted weeks receiving public transfer payments one year prior to and one or three years after entering the program, respectively, were reported. To take the potential influence of covariates into account, costs and weeks receiving public transfer payments were predicted using a generalized estimating equation (GEE) gamma regression model for repeated measures. Statistically significant difference between costs in the pre- and post-intervention period was assessed using bootstrap t-test.

We estimated health care costs per QALY gained as the ratio of change in total health care costs to change in QOL. Change in health care costs was calculated as the mean cost difference between the year prior to and the year after entering the intervention. QALYs gained was calculated as the mean difference between the EQ-5D score at baseline, before initiating the program, representing the QOL the year prior to the intervention and the EQ-5D score at 3 and 12 months calculated as 'the area under the curve' taking change over time into account, representing the QOL the year after entering the program. Data were not normal distributed and changes in costs and EQ-5D were estimated using a GEE gamma regression model for repeated measures. Raw and adjusted analyses including gender, age, marital status, ethnicity, educational level and region as covariates were conducted. In case of no convergence in the model, selected covariates were omitted.

There is no official threshold for willingness-to-pay in Denmark and we compared the health care cost per QALY to predefined willingness-to-pay thresholds of a cost-effective treatment defined by the National Institute for Health and Care Excellence (NICE) at 22,804€ (20,000£) per QALY,[25] and the widely used threshold of 43,979€ (50,000 USD) per QALY,[26]. To explore if adherence to the exercise therapy component had an impact on the results, a sub-analysis repeating all analyses restricted to patients with high compliance was conducted. All analyses were reported separately for knee and hip patients.

As previously proposed for cost-effectiveness studies and clinical trials in OA,[27,28] missing values for the EQ-5D index score at follow up were imputed using Multiple Imputations (MI) with chained equations under the assumption of data being missing at random,[29]. Since EQ-5D was not normal distributed, Predictive Mean Matching was applied, and all baseline variables presented in the study and outcome variables of interest were included in the model. In total, 40 datasets were generated, approximately equal to the largest percentages of missing observations for the outcome as recommended,[30].

Since costs for health care services delivered in municipal settings were not available, all analyses were repeated stratified for patients attending GLA:D® in private physiotherapy clinics vs. in municipal rehabilitation centers. To explore the impact of missing data, a sensitivity analysis repeating all analyses restricted to complete cases was conducted and all analyses were repeated excluding patients who died during follow up.

The significance level for all statistical analyses was defined a priori at $p<0.05$. All analyses were performed using the SAS 9.4 (SAS Institute, North Carolina, USA).

RESULTS

12,162 knee patients and 4,093 hip patients were included in the study and follow up data on EQ-5D were available for 77% immediately after treatment and 61% at one year (Figure 1). Patients with complete information had slightly better, but most likely not clinically relevant better health status at baseline compared to patients with incomplete information (Table S1, Supplementary Appendix). Baseline characteristics are presented in Table 1. Three quarters of the patients were female, median symptom duration was 2 years, almost two thirds reported use of pain medication and 31% and 4% of knee and hip patients, respectively, reported previous surgery in most affected joint.

[Figure 1]

[Table 1]

Predicted health care costs and costs for home care one year prior to and three years after entering the intervention are presented in Figure 2 and predicted public transfer payments are presented in Table 2. Additionally, mean and predicted costs one year prior to and one/three years after entering the intervention respectively are presented in Table S2 and S3, Supplementary Appendix. To take

the potential influence of covariates into account, costs are predicted for average patients, i.e. women, 65 years old, married/co-living, ethnic Danish, low educational level and living in the Capital Region. Public transfer payments are predicted for women, 55 years old, married/co-living, ethnic Danish, low educational level and living in the Capital Region since the population was restricted to adults under the age of retirement in this analysis, as public transfer payments target this age group. In the one-year horizon, monthly predicted health care costs for knee and hip patients were 263€/235€ one year prior to the intervention, rising to 331€/397€ the year after entering the program (Table S3, Supplementary Appendix). In the three year horizon, yearly predicted health care costs one year prior to the intervention were 3,392€/3,051€ for knee and hip patients, rising to 4,128€/4,473€ the third year after entering the intervention, observing the highest costs the second year post-intervention for knee patients and the first year post-intervention for hip patients (Figure 2a and 2b). The increase in mean health care costs was mainly due to costs related to surgeries in the knee or hip. On average, the raw EQ-5D score increased from 0.711 to 0.756 points for knee patients and from 0.705 to 0.747 for hip patients from baseline to one year follow up (Table 3).

[Figure 2]

[Table 2]

[Table 3]

Adjusted change in health care cost from the year prior to entering GLA:D® to the year after entering GLA:D® was 298€ (95% CI: 206-419)/640€ (400-1,009) and QALYs gained were 0.035 (0.033-0.037)/0.028 (0.025-0.032) for knee and hip patients, respectively. Hence, one-year

estimated adjusted health care costs was 8,497€ (6,242-11,324) for knee patients and 22,568€ (16,000-31,531) for hip patients per QALY gained (Table 4). Restricting the regression analysis to patients with high compliance, the one-year adjusted health care costs per QALY gained was lower; 5,438€ (2,758-9,231) for knee patients and 17,330€ (10,041-29,364) for hip patients primarily due to lower change in health care costs (Table 4). Although the upper limit of the 95% CI for hip patients was in between the two predefined willingness-to-pay thresholds, the estimated health care costs per QALY for both knee and hip patients were below both of the two predefined willingness-to-pay thresholds.

[Table 4]

Sensitivity analyses showed that knee and hip patients attending GLA:D® in a private clinic had similar health care costs per QALY but that patients attending GLA:D® in a municipal setting had higher costs for knee patients and lower costs for hip patients compared to all patients. This difference was primarily explained by different change in health care costs (Table S5, Supplementary Appendix). The complete case analysis showed lower change in health care costs and lower health care costs per QALY for knee patients (4,829€ (2,313-8,378)) but for hip patients the ratio was similar to that of all patients (Table S5, Supplementary Appendix). 53 patients died within the one-year follow up period and 11 of these within the first 3 months. Repeating all analyses excluding deaths in the regression analyses showed results similar to the main analysis (data not shown).

DISCUSSION

Our study demonstrated that an 8-week supervised patient education and exercise therapy program for knee or hip OA implemented in primary care is cost-effective in a one-year horizon with health care costs of 8,497€ per QALY for knee patients and 22,568€ for hip patients. Despite the physiotherapy visits needed to participate in the GLA:D® program, increased health care costs were primarily related to knee or hip surgeries and although the mean absolute change in health related QOL is relatively low (~0.03) the intervention is still considered cost-effective. These results support large scale implementation of GLA:D® in clinical practice.

To our knowledge this is the first study evaluating the cost-effectiveness of a combined supervised OA education and exercise therapy program with widespread implementation in primary care. Previous analyses of the GLA:D® program, but with twice the number of supervised neuromuscular exercise sessions, weight loss, insoles and pain medication if needed, have found similar results,[15,31]. A model-based study suggested that exercise therapy and education was cost-effective as compared to usual care for patients with knee or hip OA in Canada[31], while an analysis of results from a randomized trial comparing supervised exercise therapy, education and other recommended non-surgical interventions to written advice in patients with moderate to severe knee OA found the intervention to be cost-effective with incremental cost effectiveness ratios of 6,229 to 20,688 €/QALY,[15]. Our findings are also in line with other previous studies which have indicated that supervised exercise therapy alone as treatment for OA is cost-effective. Three randomized trials demonstrated that supervised exercise therapy in addition to usual care,

supplementary class-based exercise in addition to a home-based program and supervised exercise therapy compared to general practitioner care alone was likely to be cost-effective in people with knee and/or hip OA,[32-34]. Also, a model-based study estimated that adding the combination of diet and exercise therapy to usual care for overweight and obese patients with knee OA was cost-effective,[35]. Our study adds to this body of evidence, that large-scale implementation in clinical practice of a structured combined supervised education and exercise therapy program seems cost-effective in a one-year horizon.

In this study, the increased health care costs both one and three years after entering the GLA:D® program were primarily related to surgeries in the knee or hip. According to a stepwise treatment approach, joint replacement surgery is considered to be relevant in patients with end-stage OA once all appropriate non-surgical treatment options such as patient education and supervised exercise therapy of sufficient dose and length, weight loss, walking aids and pain medication have failed to reduce symptoms sufficiently,[36,37]. Existing evidence indicates that providing supervised exercise therapy can have positive impact on the number of patients having joint replacement surgery,[38-40], time to surgery,[39,40] and outcomes from surgery[41]. Ackerman et al conducted a budget impact analysis of implementing a first-line management program such as GLA:D® in Australia and demonstrated that if total knee replacement was avoided in only 1 in 12 GLA:D® participants, the program would generate cost savings,[42]. Although the lack of control group in the current study precludes analyses of avoidance of joint replacements, it highlights that regardless of surgery during follow up, supervised education and exercise therapy is cost-effective.

As a result of similar change in EQ-5D, but lower change in health care costs, health care costs per QALY were lower in patients compliant to the intervention compared to all patients enrolled in the program, indicating that the dosage of exercise therapy is important. Although we did not find that higher compliance was associated with greater effects on the EQ-5D, the lower change in health care costs in the compliant patients underlines the importance of exercise dosage as suggested by a systematic review and meta-regression analysis of 48 randomized controlled trials in patients with knee OA showing that 12 or more supervised exercise sessions are more effective than fewer supervised sessions,[43], and a systematic review and meta-analysis in patients with hip OA showing that supervised exercise therapy with high compliance with dose recommendations compared to uncertain compliance was more effective,[44]. Although dosage seems important for the effect and cost-effectiveness, knowledge of optimal exercise dosage in OA is still lacking,[9,43,45].

As there is no official threshold defining a cost-effective treatment in Denmark, we compared the health care costs per QALY to two different internationally widely used willingness-to-pay thresholds. Although the estimated health care costs per QALY for both knee and hip patients were below both of the two thresholds, the upper limit of the 95% CI for hip patients was in between the two thresholds, thus we cannot rule out that the true health care costs per QALY for hip patients is above the lower willingness-to-pay threshold (22,804€). A threshold value for willingness-to-pay for improvements in health is arbitrary and depending on the context such as budget and other treatment options,[26]. Country-level threshold value based on GDP per capita has been discussed but remains unsettled,[46]. When deciding which treatment options to implement and offer, the results from this study can support clinicians and decision-makers in terms of one-year cost-

effectiveness of supervised education and exercise therapy implemented nationwide for patients with knee and hip OA in clinical practice.

Strengths and limitations

The major strength of the study is that all costs reported are real-life costs retrieved on an individual level from a range of high-quality national registries supporting the reliability and validity of the costs,[22,47,48]. Even though it is likely that a higher level of heterogeneity in treatment protocols occurred compared to in rigorous clinical trials, another major strength is that the study included a large number of rural and urban patients with wide inclusion criteria; joint pain and functional limitations associated with OA, retrieved from a nationwide registry supporting the generalizability of the findings.

The main limitation of the study is that the study is a pre-post study where change in health care costs was evaluated against change in EQ-5D. Without a proper control group, it cannot be ruled out that the observed change in EQ-5D is related to other factors than the treatment such as regression to the mean. Also, change in costs can potentially have been affected by increasing age, since health care costs are expected to increase with increased age and accompanied morbidity,[49].

In the current study, health care costs per QALY was evaluated in a one-year horizon and additionally change in costs were reported in a three-year horizon. OA is a long-term chronic condition,[36], thus evaluating cost-effectiveness in a one-year horizon is a relatively short time

horizon warranting further long-term cost-effective analyses. However, a recent model-based cost-effectiveness analysis suggested that a physical activity program for patients with knee OA would lead to favorable long-term clinical and economic benefits,[50].

There was a loss to follow up in the GLA:D® registry and conducting a sensitivity analysis restricted to patients with complete information revealed that they had less mean change in health care costs than all included patients, indicating a risk of selective loss to follow up in the GLA:D® registry, however, the evaluation on health care costs per QALY included all patients enrolled in GLA:D®, imputing the missing outcome values at follow up. Imputing missing outcome values relied on the assumption that data were missing at random, i.e. the missingness was related to variables included in the model. However, there is a risk that loss to follow up was related to unobserved factors not available for the analysis. One third did not provide information on compliance and there is a risk that lower change in health care costs in the sub-group of patients with high compliance is affected by selection bias. However, we did not find clinically relevant health status differences at baseline among those not providing information on compliance compared to those with this information (data not shown).

The current study is based on real-world outcome data collected in nationwide physiotherapy clinics and actual health care costs retrieved from national registries, supporting the generalizability of the results. However, patients attending GLA:D® are a preselected group of patients who are commonly referred to physiotherapy for their symptoms with most being able to pay partly for the intervention, which might limit the generalizability.

CONCLUSIONS

A structured 8-week supervised education and exercise therapy program delivered in physiotherapy practice was cost-effective at one year in patients with knee and hip OA compared to conventional willingness-to-pay thresholds. Both health-related QOL and health care costs increased during the one-year time horizon, the latter mainly due to knee or hip surgeries. The results support large scale implementation of a structured supervised evidence-based patient education and exercise therapy program targeting patients with knee or hip OA and can guide clinicians and decision makers on what to expect when such programs are implemented in clinical practice.

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PATIENT AND PUBLIC INVOLVEMENT STATEMENT

Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

DATA SHARING STATEMENT

The data from the national Danish registries used in this study is available from Statistics Denmark. However, restrictions apply to the availability, as the data was used under license for the current study, and so are not publicly available. Data are however available from the authors ER and STS upon reasonable request and with permission of Statistics Denmark.

AUTHOR CONTRIBUTIONS

Study conception and design: DTG, ER, RI, JK, STS

Acquisition of data: DTG, ER, STS

Analysis and interpretation of data: DTG, ER, RI, JK, STS

Drafting the article: DTG, STS

Revising the article critically for important intellectual content: DTG, ER, RI, JK, STS

Final approval of the article: DTG, ER, RI, JK, STS

Obtaining of funding: STS

ROLE OF THE FUNDING SOURCE

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CONFLICT OF INTEREST

Dr. Roos is deputy editor of Osteoarthritis and Cartilage, the developer of the Knee injury and Osteoarthritis Outcome Score (KOOS) and several other freely available patient-reported outcome measures and co-founder of Good Life with osteoArthritis in Denmark (GLA:D®), a not-for profit initiative hosted at University of Southern Denmark aimed at implementing clinical guidelines for osteoarthritis in clinical practice.

Dr. Skou is associate editor of the Journal of Orthopaedic & Sports Physical Therapy, has received grants from The Lundbeck Foundation, personal fees from Munksgaard, all of which are outside the submitted work. He is co-founder of GLA:D®.

R Ibsen: None

J Kjellberg: None

Dr. Grønne is employed as data manager in the GLA:D® project.

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TABLE LEGENDS

Table 1. Baseline characteristics in knee and hip patients attending GLA:D®

Table 2. Predicted public transfer payments one year prior to and one or three years following GLA:D® for knee and hip patients

Table 3. Change in health-related quality of life from baseline to 12 months for knee and hip patients attending GLA:D®

Table 4. Adjusted and raw estimated health care costs per QALY from baseline to 12 months for all knee and hip patients attending GLA:D® and for knee and hip patients with high compliance

Table 1. Baseline characteristics in knee and hip patients attending GLA:D®

	Knee (n: 12,162)	Hip (n: 4,093)
Age (years), mean (SD)	64.1 (9.8)	65.7 (9.4)
Gender (Female), % (n)	73.1 (8,887)	73.6 (3,014)
BMI (kg/m^2), mean (SD)	28.6 (5.3)	26.9 (4.6)
Marital status, % (n)		
Married or living with others	72.4 (8,803)	70.7 (1,079)
Single	27.6 (3,359)	29.3 (1,200)
Ethnic background, % (n)		
Danish	96,2 (11,701)	96.8 (3,961)
Other western	2.5 (299)	2.6 (106)
Not western	1.3 (160)	0.6 (25)
Educational level, % (n)		
Primary	18.7 (2,277)	19.7 (1,493)
Secondary	3.0 (367)	2.7 (112)
Vocational	39.1 (4,761)	36.2 (1,481)
Short-term	4.6 (558)	4.5 (185)
Bachelor	26.2 (3,186)	28.0 (1,145)
Long-term	7.2 (873)	8.0 (329)
Unknown	1.2 (140)	0.9 (35)
Social status, % (n)		
Employed	43.3 (5,264)	36.5 (1,493)
Unemployed	2.1 (256)	1.5 (61)
Sick pay (public funded)	0.7 (86)	0.4 (15)
Disability pension	3.7 (444)	3.7 (152)
Early retirement	6.3 (766)	7.3 (297)
Age pension	42.8 (5,209)	49.5 (2,028)
Other	1.1 (137)	1.1 (47)
Administrative region, % (n)		
Capital Region	27.7 (3,367)	27.6 (1,131)
Region Zealand	13.0 (1,578)	13.1 (535)
Region of Southern Denmark	21.8 (2,654)	25.2 (1,030)
Central Denmark Region	25.4 (3,085)	24.9 (1,021)
North Denmark Region	12.2 (1,478)	9.2 (376)
Number of comorbidities[%], % (n)		
0	38.2 (4,367)	39.7 (1,533)
1	35.7 (4,076)	35.1 (1,358)
2	17.3 (1,979)	16.8 (649)
3 or more	8.8 (1.006)	8.4 (326)
Symptom duration (months), median (IQR)	24 (7-60)	24 (8-48)
Pain intensity (VAS 0-100, best to worst), mean (SD)	48.6 (22.0)	47.6 (21.7)
Bilateral symptoms, % (n)	46.3 (5,614)	26.1 (1,064)
Walk speed[#] (m/sec), mean (SD)	1.49 (0.33)	1.49 (0.34)
Previous surgery in worst joint[&], % (n)	30.7 (3,725)	4.0 (161)
Use of pain medication[¤] (yes), % (n)		
Overall	61.3 (7,431)	64.2 (2,629)
Paracetamol	49.9 (6,073)	53.3 (2,184)
NSAIDs	35.6 (4,325)	34.6 (1,419)
Opioids	7.1 (868)	9.0 (367)
KOOS/HOOS QOL[*] (0-100, best to worst), mean (SD)	45.2 (14.7)	47.4 (15.1)

Missing values: BMI n: 5 (knee), n: 7 (hip); Number of comorbidities n: 711 (knee), n: 215 (hip); Symptom duration (mainly missing due to technical problems): n: 3.157 (knee), n: 1,096 (hip) ; Pain intensity: n:23 (knee), n:9 (hip) ; Bilateral symptoms: n:32 (knee), n:20 (hip) ; Walk speed: n:610 (knee), n:221 (hip); KOOS/HOOS QOL: n: 36 (knee),

n: 21 (hip).

[#]Walking speed was assessed with the 40 m Fast-paces Walk Test under instruction of the GLA:D®-therapist

[¤]Self-reported use of pain medication during last 3 months

[%]Number of comorbidities calculated from self-report of the following conditions: hypertension, cardiovascular diseases, lung diseases, diabetes, stomach diseases, liver- or kidney diseases, blood diseases, cancer, depression, rheumatoid arthritis, neurological disorders, other medical diseases

[&]Self-reported previous surgery in worst joint

[*]Knee injury and Osteoarthritis Outcome Score or Hip disability or Osteoarthritis Outcome Score Quality Of Life sub-scale score

672 **Table 2. Predicted public transfer payments one year prior to and one or three years following GLAD® for knee and hip patients**

	One-year horizon							Three-year horizon						
	Pre-period (1 year)	Post-period (mth 1-3)		Post-period (mth 4-12)		Post-period (year 1)		Pre-period (1 year)	Post-period (year 1)		Post-period (year 2)		Post-period (year 3)	
	Weeks/ month	Weeks/ month	p-value	Weeks/ month	p-value	Weeks/ month	p-value	Weeks/ year	Weeks/ year	p-value	Weeks/ year	p-value	Weeks/ year	p-value
	Knee patients in workforce (n: 5,586)							Knee patients in workforce (n: 905)						
Public transfer payments[#]														
Unemployed	0.24	0.26	0.000	0.27	0.001	0.27	0.000	3.50	3.82	0.314	3.51	0.986	3.32	0.703
Sheltered employment	0.10	0.10	0.959	0.10	0.967	0.10	0.982	1.61	1.59	0.927	1.69	0.671	1.78	0.422
Sick pay	0.13	0.16	0.000	0.14	0.164	0.15	0.029	1.47	1.70	0.295	1.54	0.789	1.16	0.201
Rehabilitation	0.01	0.01	0.254	0.01	0.494	0.01	0.407	0.09	0.03	0.017	0.09	0.960	0.06	0.731
Education	0.01	0.00	0.136	0.01	0.950	0.00	0.770	0.20	0.18	0.907	0.23	0.690	0.20	0.991
Disability pension	0.23	0.24	0.006	0.23	0.259	0.24	0.136	6.02	6.02	0.969	5.91	0.467	6.00	0.966
Early retirement	0.37	0.46	0.000	0.46	0.000	0.46	0.000	6.06	7.35	0.000	7.02	0.071	5.44	0.354
	Hip patients in workforce (n: 1,543)							Hip patients in workforce (n: 264)						
Public transfer payments[§]														
Unemployed	0.19	0.19	0.540	0.20	0.309	0.20	0.325	3.36	3.56	0.730	3.20	0.865	2.90	0.672
Sheltered employment	0.10	0.10	0.458	0.10	0.516	0.10	0.470	1.92	1.80	0.712	1.50	0.217	1.73	0.661
Sick pay	0.10	0.13	0.082	0.16	0.001	0.15	0.003	1.38	2.00	0.127	1.41	0.967	1.32	0.903
Rehabilitation	0.00	0.01	0.202	0.00	0.407	0.00	0.812	0.04	0.06	0.000	0.19	0.000	0.41	0.000
Education	0.01	0.01	0.321	0.01	0.659	0.01	0.557	0.27	0.20	0.393	0.20	0.598	0.12	0.183
Disability pension	0.29	0.26	0.264	0.27	0.502	0.27	0.427	3.81	3.92	0.501	3.66	0.673	3.29	0.171
Early retirement	0.47	0.59	0.000	0.58	0.000	0.58	0.000	9.02	11.54	0.000	10.01	0.422	7.11	0.219

673 [#]Predicted weeks receiving public transfer payments in one-year horizon for women, 55 years, married/co-living, Danish ethnicity, low education and living in the
674 Capital Region estimated using a generalized estimating equation gamma regression model for repeated measures including sex, age, marital status, ethnicity,
675 education and region as covariates. Because of no convergence in the model following covariates were omitted: 'Early retirement': sex, marital status, ethnicity,
676 education and region; 'Rehabilitation': age, marital status, ethnicity and education; 'Education': age, marital status, ethnicity and education. Predicted weeks receiving
677 public transfer payments in three-year horizon for women, 55 years and low education estimated using a generalized estimating equation gamma regression model for
678 repeated measures including sex, age and education as covariates. Because of no convergence in the model following covariates were omitted: 'Sheltered
679 employment': sex and education; Disability pension'': sex and education; 'Early retirement': age.
680 [§]Predicted weeks receiving public transfer payments in one-year horizon for women, 55 years, married/co-living, Danish ethnicity, low education and living in the
681 Capital Region estimated using a generalized estimating equation gamma regression model for repeated measures including sex, age, marital status, ethnicity,
682 education and region as covariates. Because of no convergence in the model following covariates were omitted: 'Early retirement': sex, marital status, ethnicity,
683 education and region; 'Rehabilitation': age, marital status, ethnicity, education and region; 'Education': age, marital status, ethnicity, education and region. Predicted
684 weeks receiving public transfer payments in three-year horizon for women, 55 years and low education estimated using a generalized estimating equation gamma
685 regression model for repeated measures including sex, age and education as covariates. Because of no convergence in the model following covariates were omitted:

‘Sheltered employment’: sex and education; Disability pension’’: sex and education; ‘Early retirement’: age; ‘Rehabilitation’: sex, age and education; ‘Rehabilitation: sex, age and education.

Table 3. Change in health-related quality of life from baseline to 12 months for knee and hip patients attending GLA:D®

	Knee (n: 12,162)				Hip (n: 4,093)			
	Pre period QALY (Baseline EQ-5D)	**3 months EQ-5D§**	**12 months EQ-5D§**	**Post period QALY#**	**Pre period QALY** (Baseline EQ-5D)	**3 months EQ-5D§**	**12 months EQ-5D§**	**Post period QALY#**
Mean	0.711	0.752	0.756	0.748	0.705	0.733	0.747	0.735
SD	0.113	0.121	0.134	0.107	0.110	0.127	0.144	0.108

§Missing observations for EQ-5D at 3 and 12 months were imputed by Multiple Imputations

#One year post period QALY was calculated as the area under the curve taking both 3- and 12-months measurements into account

Table 4. Adjusted and raw estimated health care costs per QALY from baseline to 12 months for all knee and hip patients attending GLA:D® and for knee and hip patients with high compliance

	Knee			Hip		
	Change in health care costs (€) (95 % CI)	**Change in EQ-5D (QALYs) (95 % CI)§**	**Euro pr. QALY (95 % CI)§**	**Change in health care costs (€) (95 % CI)**	**Change in EQ-5D (QALYs) (95 % CI)§**	**Euro pr. QALY (95 % CI)§**
Adjusted#	298 (206-419)	0.035 (0.033-0.037)	8,497 (6,242–11,324)	640 (400-1,009)	0.028 (0.025-0.032)	22,568 (16,000-31,531)
Unadjusted	895 (719-1,088)	0.037	24,236	2,162 (1,723-2,671)	0.030	71,478
High compliance#,¤	197 (91-360)	0.036 (0.033-0.039)	5,438 (2,758-9,231)	492 (241-969)	0.028 (0.024-0.033)	17,330 (10,041-29,364)

§Confidence Interval not generated from the MI

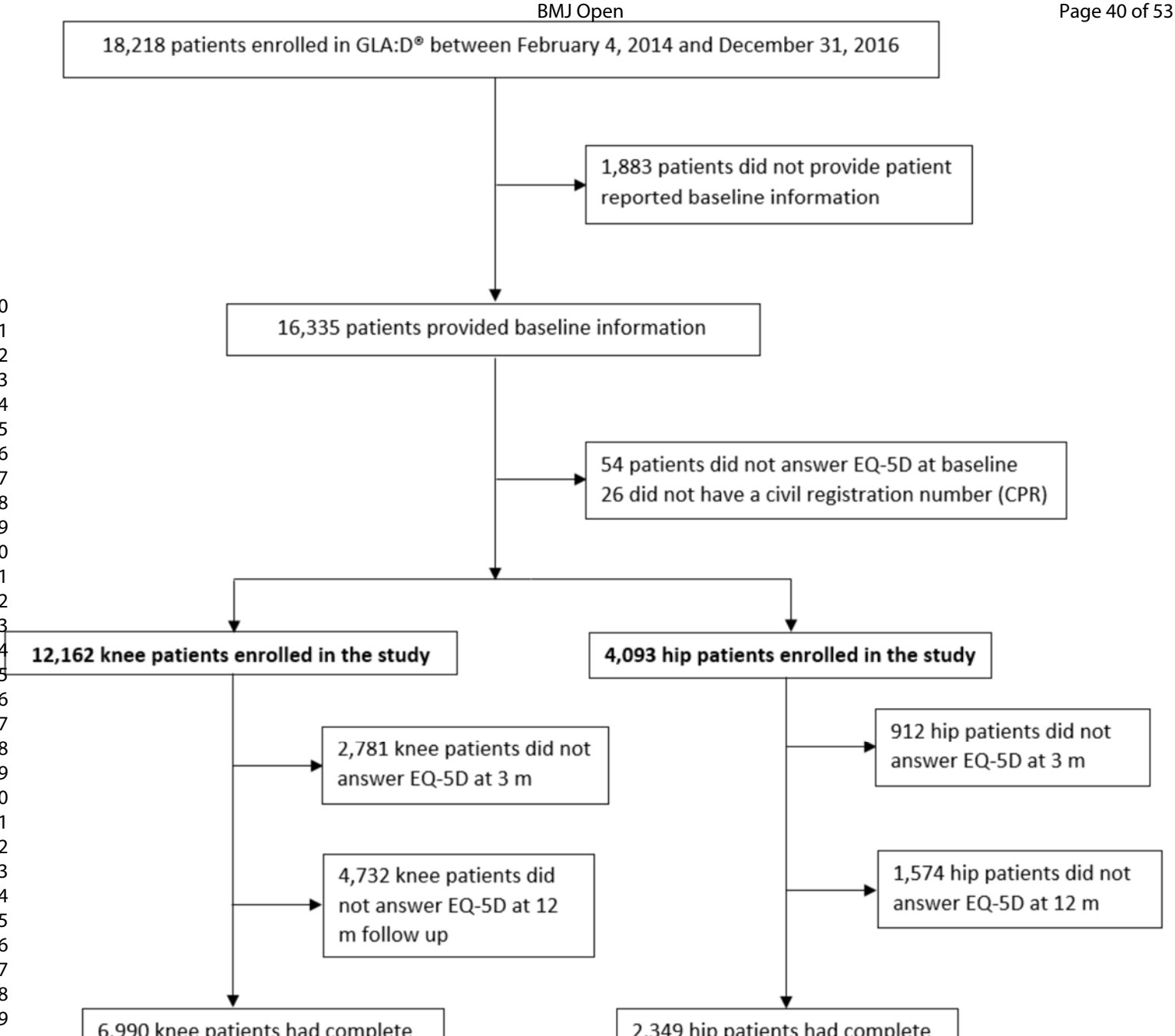
#Adjusted for age, gender, marital status, ethnicity, educational level and region

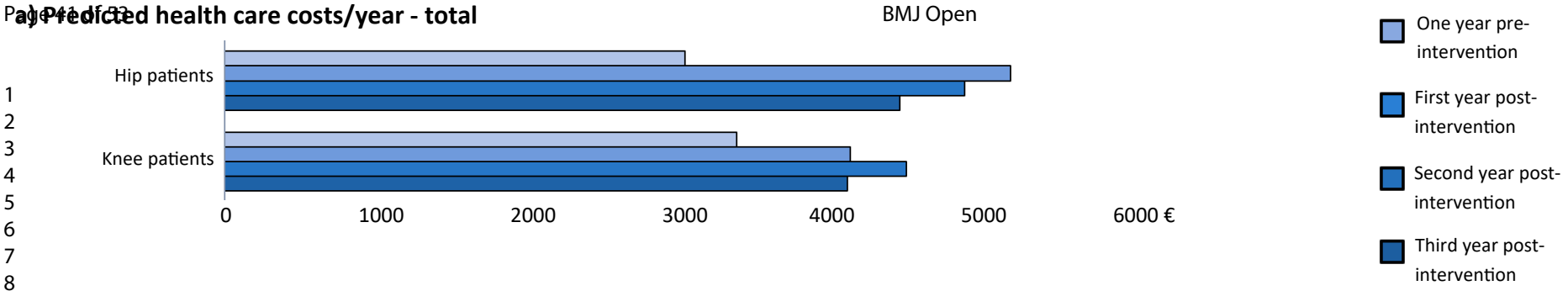
¤High compliance group defined as patients attending minimum 10 supervised exercise sessions

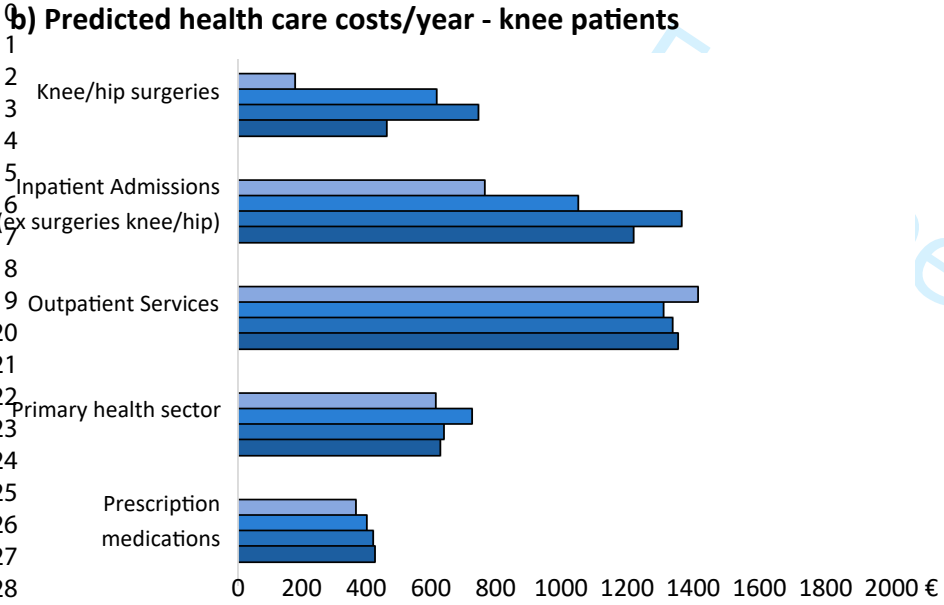
FIGURE LEGENDS

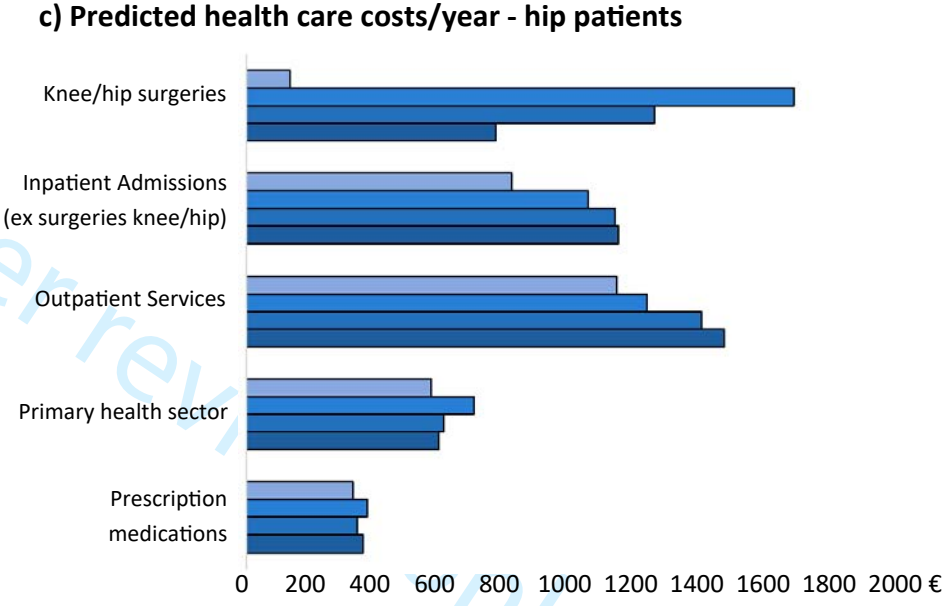
Figure 1. Flow chart

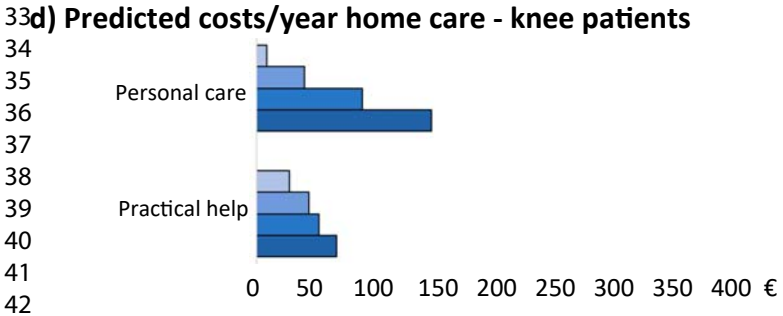
Figure 2. Predicted healthcare costs and home care costs one year prior to and up to three years following GLA:D® for knee and hip patients

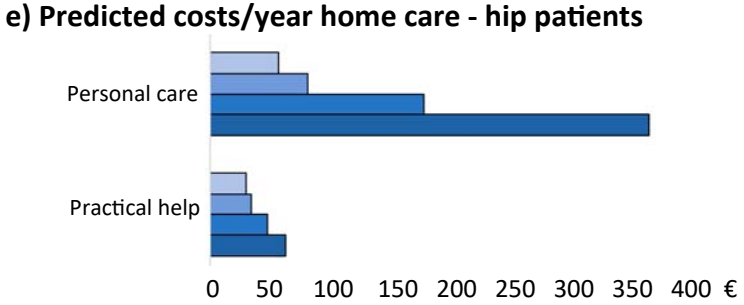

18,218 patients enrolled in GLA:D® between February 4, 2014 and December 31, 2016
1,883 patients did not provide patient reported baseline information
16,335 patients provided baseline information
54 patients did not answer EQ-5D at baseline
26 did not have a civil registration number (CPR)
12,162 knee patients enrolled in the study
4,093 hip patients enrolled in the study
2,781 knee patients did not answer EQ-5D at 3 m
912 hip patients did not answer EQ-5D at 3 m
4,732 knee patients did not answer EQ-5D at 12 m follow up
1,574 hip patients did not answer EQ-5D at 12 m
6,990 knee patients had complete information on EQ-5D
2,349 hip patients had complete information on EQ-5D











Predicted health care costs and costs for home care in three-year horizon for women, 65 years, married/co-living and low education estimated using a generalized estimating equation gamma regression model for repeated measures including sex, age, and education. Because of no convergence in the model age and education were omitted estimating costs for home care.

Supplementary Appendix

Table S1: Baseline characteristics in patients with complete information and patients with loss to follow up

Table S2: Mean health care costs and home care costs one year prior to and one or three years following GLA:D® for knee and hip patients

Table S3: Predicted health care costs and home care costs one year prior to and one or three years following GLA:D® for knee and hip patients

Table S4: Mean public transfer payments one year prior to and one or three years following GLA:D® for knee and hip patients

Table S5. Sensitivity analysis - adjusted estimated health care cost per QALY from baseline to 12 months for knee and hip patients attending GLA:D® in private clinics, municipal clinics and patients with complete information

Table S1: Baseline characteristics in patients with complete information and patients who had incomplete information

	Complete information		Incomplete information	
	Knee (n: 6,990)	Hip (n: 2,349)	Knee (n: 5,173)	Hip (n: 1,749)
Age (years), mean (SD)	64.4 (9.1)	65.7 (8.7)	63.7 (10.7)	65.7 (10.3)
Gender (Female), % (n)	73.2 (5,113)	74.6 (1,753)	73.0 (3,777)	72.2 (1,263)
BMI (kg/m^2), mean (SD)	28.4 (5.2)	26.6 (4.4)	28.9 (5.4)	27.2 (4.9)
Marital status, % (n)				
Married or living with others	75 (5,256)	73 (1,714)	69 (3,547)	68 (1,179)
Single	25 (1,730)	27 (634)	31 (1,629)	32 (566)
Ethnic background, % (n)				
Danish	97 (6,773)	97 (2,276)	95 (4,928)	97 (1,685)
Other western	2 (160)	3 (60)	3 (139)	3 (46)
Not western	1 (53)	0.5 (11)	2 (107)	0.8 (14)
Educational level, % (n)				
Primary	17 (1,177)	18 (420)	21 (1,100)	22 (386)
Secondary	3 (197)	3 (69)	3 (170)	2 (43)
Vocational	38 (2,671)	34 (792)	40 (2,090)	39 (689)
Short-term	5 (322)	5 (123)	5 (236)	4 (62)
Bachelor	28 (1,999)	31 (722)	31 (1,187)	24 (423)
Long-term	8 (546)	9 (200)	9 (327)	7 (129)
Unknown	1 (74)	1 (22)	1 (66)	1 (13)
Social status, % (n)				
Employed	44 (3,012)	37 (866)	44 (2,252)	37 (627)
Unemployed	0.5 (35)	0.3 (6)	0.8 (42)	0.4 (7)
Sick pay (public funded)	0.5 (37)	0.4 (9)	1 (49)	0.3 (6)
Disability pension	3 (228)	3 (76)	4 (216)	4 (76)
Early retirement	8 (527)	9 (2025)	5 (239)	6 (95)
Age pension	43 (3,006)	49 (1,137)	43 (2,203)	52 (891)
Other	1 (69)	1 (33)	1 (68)	0.8 (14)
Sick leave[!], % (n)	4.9 (314)	3.2 (77)	6.8 (353)	3.8 (67)
Administrative region, % (n)				
Capital Region	27 (1,875)	26 (606)	29 (1,492)	30 (525)
Region Zealand	13 (936)	14 (327)	12 (642)	12 (208)
Region of Southern Denmark	23 (1,579)	26 (602)	21 (1,075)	25 (428)
Central Denmark Region	26 (1,796)	26 (609)	25 (1,275)	24 (412)
North Denmark Region	11 (800)	9 (204)	13 (1,289)	10 (172)
Number of comorbidities[%], % (n)				
0	39.2 (2,575)	41.9 (928)	36.9 (1,798)	36.5 (608)
1	36.2 (2,381)	35.5 (787)	35.0 (1,704)	34.7 (578)
2	17.0 (1,118)	15.8 (350)	17.8 (867)	18.1 (302)
3 or more	7.7 (504)	6.9 (152)678	10.4 (505)	10.7 (178)
Symptom duration (months), median (IQR)	24 (7-60)	24 (8-48)	24 (7-60)	24 (8-48)
Pain intensity (VAS 0-100, best to worst), mean (SD)	47.3 (21.8)	45.9 (21.4)	50.3 (22.3)	49.7 (22.0)
Bilateral symptoms, % (n)	46.7 (3,259)	26.6 (622)	45.7 (2,355)	25.4 (442)
Walk speed[#] (m/sec), mean (SD)	1.51 (0.32)	1.52 (0.33)	1.46 (0.35)	1.45 (0.35)

Previous surgery in worst joint[&], % (n)	30.2 (2,112)	3.2 (78)	31.3 (1,619)	4.8 (84)
Receive home care, % (n)	8.9 (621)	9.6 (224)	11.5 (593)	12.4 (215)
Use of pain medication[¤] (yes), % (n)				
Overall	60.9 (4,256)	62.7 (1,473)	61.8 (3,196)	66.1 (1,156)
Paracetamol	49,5 (3,463)	52.9 (1,243)	50.5 (2,610)	53.8 (941)
NSAIDs	35.8 (2,504)	32.5 (764)	35,2 (1,1821)	37.5 (655)
Opioids	6.6 (459)	8.1 (190)	7.9 (409)	10.1 (177)
KOOS/HOOS QOL[*] (0-100, best to worst), mean (SD)	46.0 (14.5)	47.9 (15.0)	44.1 (15.0)	46.7 (15.3)

Missing values: BMI: n: 2 (knee, complete), n: 5 (hip, complete), n: 3 (knee, incomplete), n: 2 (hip, incomplete); Ethnic background: n: 1 (hip, complete), n: 2 (knee, incomplete); Social status: n: 72 (knee, complete), n: 19 (hip, complete), n: 107 (knee, incomplete), n: 29 (hip, incomplete); Sick leave: n: 6 (knee, complete), n: 1 (hip, complete), n: 19 (knee, incomplete), n: 3 (hip, incomplete); Number of comorbidities: n: 412 (knee, complete), n: 132 (hip, complete), n: 299 (knee, incomplete), n: 83 (hip, incomplete); Symptom duration (mainly missing due to technical problems): n: 1.730 (knee, complete), n: 595 (hip, complete), n: 1.427 (knee, incomplete), n: 501 (hip, incomplete); Pain intensity: n: 8 (knee, complete), n: 3 (hip, complete), n: 15 (knee, incomplete), n: 6 (hip, incomplete); Bilateral symptoms: n: 14 (knee, complete), n: 10 (hip, complete), n: 18 (knee, incomplete), n: 10 (hip, incomplete); Walk speed: n: 309 (knee, complete), n: 100 (hip, complete), n: 301 (knee, incomplete), n: 121 (hip, incomplete); Receive home care: n: 31 (knee, complete), n: 8 (hip, complete), n: 36 (knee, incomplete), n: 8 (hip, incomplete); KOOS/HOOS QOL: n: 17 (knee, complete), n: 9 (hip, complete), n: 19 (knee, incomplete), n: 10 (hip, incomplete).

[#]Walking speed was assessed with the 40 m Fast-paces Walk Test under instruction of the GLA:D®-therapist

[¤]Self-reported use of pain medication during last 3 months

[!]Self-reported sick leave for more than 1 month during last year due to knee/hip

[%]Number of comorbidities calculated from self-report of the following conditions: hypertension, cardiovascular diseases, lung diseases, diabetes, stomach diseases, liver- or kidney diseases, blood diseases, cancer, depression, rheumatoid arthritis, neurological disorders, other medical diseases

[&]Self-reported previous surgery in worst joint

[*]Knee injury and Osteoarthritis Outcome Score or Hip disability or Osteoarthritis Outcome Score Quality Of Life sub-scale score

33 **Table S2. Mean health care costs and home care costs one year prior to and one or three years following GLAD® for knee and hip patients**

	Pre-period (1 year)	Post-period (mth 1-3)		Post-period (mth 4-12)		Post-period (1 year)		Pre-period (1 year)	Post-period (year 1)		Post-period (year 2)		Post-period (year 3)	
	Cost (€/month)	Cost (€/month)	p-value	Cost (€/month)	p-value	Cost (€/month)	p-value	Cost (€/Year)	Cost (€/year)	p-value	Cost (€/year)	p-value	Cost (€/year)	p-value
	Knee (n: 12,162)							Knee (n: 1,879)						
Health costs (somatic)														
Inpatient Admissions total	**73.1**	**67.7**	0.999	**170.6**	0.000	**144.8**	0.000	**962.1**	**1,785.3**	0.000	**2,086.1**	0.000	**1,729.7**	0.000
Thereof inpatient														
Surgery knee/hip	9.6	17.9	0.004	67.7	0.000	55.2	0.000	160.0	618.4	0.000	681.6	0.000	428.7	0.000
Surgery other	11.3	4.9	0.000	14.1	0.596	11.8	1.000	151.3	225.5	0.866	198.8	0.995	290.1	1.000
Outpatient Services total	**108.4**	**90.3**	0.000	**107.4**	1.000	**103.1**	0.764	**1,421.0**	**1,345.1**	1.000	**1,359.0**	1.000	**1,372.1**	0.771
Thereof outpatient														
Surgery knee/hip	4.3	1.2	0.000	1.7	0.000	1.6	0.000	74.9	16.9	0.000	10.0	0.000	6.0	0.000
Surgery other	1.9	1.8	1.000	1.8	1.000	1.8	1.000	23.4	15.5	0.998	24.4	1.000	32.1	1.000
Primary health sector total	**48.9**	**75.5**	0.000	**49.6**	0.963	**56.1**	0.000	**562.7**	**669.7**	0.000	**593.8**	0.614	**581.8**	0.000
Thereof primary														
Physiotherapy	5.2	33.7	0.000	7.7	0.000	14.2	0.000	66.2	175.4	0.000	68.5	1.000	60.8	0.000
Chiropractic	0.5	0.5	1.000	0.5	0.768	0.5	0.946	6.2	6.9	0.999	6.0	1.000	5.7	0.942
General practitioner	18.5	16.7	0.000	17.5	0.000	17.3	0.000	215.8	206.4	0.783	222.9	0.977	221.1	0.000
Other primary	24.7	24.5	1.000	23.9	0.560	24.0	0.816	274.6	281.0	1.000	296.3	0.809	294.2	0.818
Prescription medications total	**28.8**	**29.5**	0.998	**29.9**	0.873	**29.8**	0.943	**314.5**	**346.9**	0.782	**367.7**	0.161	**372.8**	0.938
Thereof prescription														
Painkiller medications	3.4	3.6	1.000	3.8	0.985	3.7	0.995	34.8	38.4	0.940	40.2	0.616	39.3	0.996
Not painkiller medications	25.4	25.9	1.000	26.2	0.982	26.1	0.993	279.8	308.5	0.869	327.5	0.252	333.5	0.994
Health costs total (somatic)	**259.2**	**263.0**	1.000	**357.6**	0.000	**333.8**	0.000	**3,260.3**	**4,147.0**	0.001	**4,406.6**	0.000	**4,056.4**	0.000
Home care														
Home care total	**2.5**	**3.2**	0.851	**4.6**	0.001	**4.2**	0.002	**30.7**	**60.1**	0.718	**107.7**	0.016	**203.3**	0.015
Thereof home care														
Home care – Care	1.0	1.6	0.965	2.5	0.008	2.2	0.013	8.3	29.8	0.756	69.4	0.019	151.7	0.147
Home care - Practical help	1.5	1.7	0.974	2.1	0.078	2.0	0.141	22.4	30.3	0.982	38.4	0.390	51.7	0.003
	Hip (n: 4,093)							Hip (n: 658)						
Health costs (somatic)														
Inpatient Admissions total	**79.8**	**127.1**	0.000	**274.4**	0.000	**237.4**	0.000	**1,099.4**	**3,047.2**	0.000	**2,699.7**	0.000	**2,141.7**	0.000
Thereof inpatient														
Surgery knee/hip	13.0	77.2	0.000	181.5	0.000	155.3	0.000	162.5	1,901.2	0.000	1,391.5	0.000	901.2	0.000
Surgery other	6.8	2.7	0.198	10.4	0.732	8.4	0.998	95.8	122.7	1.000	131.9	1.000	137.1	0.999
Outpatient Services total	**96.4**	**87.0**	0.676	**114.8**	0.040	**107.8**	0.453	**1,169.9**	**1,259.9**	1.000	**1,420.9**	0.947	**1,478.7**	0.463
Thereof outpatient														
Surgery knee/hip	0.3	0.7	0.999	0.9	0.750	0.8	0.661	6.8	9.9	1.000	0.0	0.996	0.0	0.673
Surgery other	1.7	3.0	0.855	2.2	0.996	2.4	0.874	28.2	18.3	1.000	17.1	0.999	15.0	1.000
Primary health sector total	**49.1**	**79.9**	0.000	**51.9**	0.000	**58.9**	0.000	**571.3**	**701.2**	0.000	**611.1**	0.934	**594.4**	0.000
Thereof primary														
Physiotherapy	6.4	37.5	0.000	8.8	0.000	16.0	0.000	89.6	208.1	0.000	91.3	1.000	72.0	0.000
Chiropractic	0.7	0.5	0.031	0.5	0.001	0.5	0.001	8.1	7.2	1.000	4.6	0.034	6.4	0.002
General practitioner	18.0	16.9	0.041	17.9	1.000	17.7	0.970	206.9	205.7	1.000	233.1	0.759	218.7	0.972
Other primary	23.9	24.9	0.983	24.7	0.993	24.7	0.986	266.6	280.3	1.000	292.1	0.973	297.3	0.988
Prescription medications total	**28.7**	**29.6**	1.000	**30.3**	1.000	**30.1**	0.977	**316.9**	**358.8**	0.989	**335.2**	1.000	**349.8**	0.980
Thereof prescription														
Painkiller medications	3.1	4.1	0.000	3.9	0.000	4.0	0.000	33.4	44.6	0.530	37.1	1.000	35.8	0.000
Not painkiller medications	25.7	25.6	1.000	26.3	1.000	26.1	1.000	283.5	314.2	1.000	298.1	1.000	314.0	1.000
Health costs total (somatic)	**254.1**	**323.6**	0.000	**471.5**	0.000	**434.2**	0.000	**3,157.5**	**5,367.0**	0.000	**5,066.9**	0.000	**4,564.6**	0.000
Home care														
Home care total	**3.4**	**4.0**	1.000	**4.9**	0.977	**4.7**	0.994	**78.3**	**108.9**	1.000	**189.1**	1.000	**265.0**	0.994
Thereof home care														
Home care – Care	1.8	2.1	1.000	2.7	0.999	2.6	1.000	53.1	79.5	1.000	152.3	0.995	218.6	1.000
Home care - Practical help	1.6	1.9	1.000	2.2	0.710	2.1	0.869	25.2	29.3	1.000	36.8	0.999	46.4	0.994

34 **Table S3. Predicted health care costs and home care costs one year prior to and one or three years following GLA:D® for knee and hip patients**

	One-year horizon							Three-year horizon						
	Pre-period (1 year)	Post-period (mth 1-3)		Post-period (mth 4-12)		Post-period (year1)		Pre-period (1 year)	Post-period (year 1)		Post-period (year 2)		Post-period (year 3)	
	Cost (€/month)	Cost (€/month)	p-value	Cost (€/month)	p-value	Cost (€/month)	p-value	Cost (€/Year)	Cost (€/year)	p-value	Cost (€/year)	p-value	Cost (€/year)	p-value
	Knee[#]							Knee[§]						
Health costs (somatic)														
Inpatient Admissions total	**70.2**	**61.6**	0.097	**159.9**	0.000	**135.2**	0.000	**935.1**	**1,657.4**	0.000	**2,105.4**	0.000	**1,671.9**	0.000
Thereof inpatient														
Surgery knee/hip	9.1	17.5	0.000	68.2	0.000	55.5	0.000	176.2	610.9	0.000	739.9	0.000	456.0	0.000
Surgery other	8.9	3.9	0.002	10.1	0.340	8.5	0.767	112.1	152.2	0.318	153.9	0.294	211.4	0.052
Outpatient Services total	**105.7**	**86.7**	0.000	**103.0**	0.328	**98.9**	0.006	**1,415.7**	**1,307.8**	0.273	**1,337.8**	0.486	**1,352.6**	0.515
Thereof outpatient														
Surgery knee/hip	0.7	0.2	0.000	0.3	0.000	0.3	0.000	80.6	17.8	-	7.4	-	6.7	-
Surgery other	1.7	1.5	0.692	1.4	0.370	1.5	0.376	25.4	18.8	0.453	28.8	0.736	38.0	0.291
Primary health sector total	**59.4**	**92.4**	0.000	**60.3**	0.041	**68.3**	0.000	**608.8**	**720.2**	0.000	**632.4**	0.031	**621.8**	0.275
Thereof primary														
Physiotherapy	6.5	42.5	0.000	9.5	0.000	17.7	0.000	70.0	190.5	0.000	71.8	0.584	64.3	0.103
Chiropractic	0.5	0.5	0.144	0.5	0.004	0.5	0.003	5.7	6.3	0.221	5.6	0.870	5.1	0.264
General practitioner	18.3	16.5	0.000	17.3	0.000	17.1	0.000	235.4	223.5	0.002	240.2	0.256	238.6	0.468
Other primary	33.7	33.8	0.874	32.8	0.029	33.1	0.082	297.9	298.9	0.904	314.6	0.066	313.6	0.118
Prescription medications total	**29.5**	**30.4**	0.008	**30.6**	0.000	**30.6**	0.000	**363.0**	**396.8**	0.000	**415.2**	0.000	**419.3**	0.000
Thereof prescription														
Painkiller medications	3.5	3.8	0.000	3.9	0.000	3.9	0.000	43.2	47.9	0.001	49.8	0.001	49.2	0.004
Not painkiller medications	25.8	26.3	0.061	26.5	0.003	26.4	0.003	318.8	348.1	0.000	364.3	0.000	368.6	0.000
Health costs total (somatic)	**263.3**	**263.7**	0.952	**354.0**	0.000	**331.3**	0.000	**3,391.7**	**4,146.2**	0.000	**4,518.3**	0.000	**4,127.5**	0.000
Home care														
Home care total	**2.7**	**3.6**	0.029	**5.0**	0.001	**4.6**	0.001	**35.5**	**77.2**	**0.011**	**131.1**	0.000	**214.6**	0.000
Thereof home care														
Home care – Care	0.9	1.4	0.004	2.1	0.082	2.0	0.153	8.5	41.1	0.014	90.2	0.000	149.0	0.000
Home care - Practical help	1.8	2.2	0.029	2.8	0.000	2.6	0.000	28.1	44.5	0.052	53.0	0.001	68.1	0.000
	Hip[#]							Hip[§]						
Health costs (somatic)														
Inpatient Admissions total	**71.7**	**111.3**	0.000	**243.2**	0.000	**208.9**	0.000	**978.4**	**2,818.4**	0.000	**2,461.1**	0.000	**1,966.0**	0.006
Thereof inpatient														
Surgery knee/hip	11.6	67.0	0.000	167.5	0.000	142.3	0.000	138.1	1,734.6	0.000	1,294.2	0.000	788.5	0.000
Surgery other	6.9	1.3	0.001	11.8	0.086	9.2	0.353	89.2	145.3	0.342	129.6	0.465	139.2	0.370
Outpatient Services total	**77.1**	**68.9**	0.006	**91.2**	0.000	**85.4**	0.012	**1,174.6**	**1,270.1**	0.401	**1,441.3**	0.074	**1,513.5**	0.038
Thereof outpatient														
Surgery knee/hip[&]	0.0	0.0	0.238	0.2	0.000	0.1	0.000	-	-		-		-	
Surgery other	0.4	0.3	0.799	0.4	0.927	0.4	0.881	37.7	29.6	0.643	24.5	0.383	22.1	0.395
Primary health sector total	**58.7**	**96.3**	0.000	**62.4**	0.000	**70.9**	0.000	**584.9**	**719.9**	0.000	**625.2**	0.021	**608.4**	0.231
Thereof primary														
Physiotherapy	8.1	47.7	0.000	11.0	0.000	20.2	0.000	94.5	221.7	0.000	96.4	0.805	74.8	0.003
Chiropractic	0.5	0.4	0.000	0.4	0.000	0.4	0.000	8.9	7.3	0.143	4.9	0.000	6.6	0.144
General practitioner	17.3	16.3	0.000	17.2	0.346	16.9	0.019	214.1	212.0	0.728	228.4	0.020	224.9	0.120
Other primary	32.4	33.9	0.120	34.0	0.038	33.9	0.029	269.0	283.3	0.386	294.0	0.098	300.4	0.056
Prescription medications total	**28.3**	**28.9**	0.333	**29.6**	0.005	**29.4**	0.023	**337.5**	**381.9**	0.016	**350.5**	0.642	**368.7**	0.298
Thereof prescription														
Painkiller medications	2.9	3.8	0.000	3.7	0.000	3.7	0.000	38.0	49.2	0.000	41.8	0.189	41.5	0.327
Not painkiller medications	25.2	24.8	0.452	25.7	0.330	25.4	0.747	298.0	332.1	0.058	306.2	0.766	324.5	0.365
Health costs total (somatic)	**234.5**	**297.6**	0.000	**433.0**	0.000	**397.3**	0.000	**3,051.0**	**5,207.7**	0.000	**4,902.1**	0.000	**4,473.4**	0.001
Home care														
Home care total	**1.1**	**1.7**	0.255	**1.9**	0.009	**1.9**	0.009	**82.4**	**111.4**	0.012	**214.5**	0.000	**406.0**	0.041
Thereof home care														
Home care – Care	0.3	0.3	0.881	0.4	0.195	0.4	0.264	55.1	79.1	0.099	173.3	0.062	356.3	0.064

Home care - Practical help	1.1	1.4	0.067	1.7	0.010	1.7	0.008	28.7	33.1	0.001	46.1	0.000	61.0	0.012

[#]Predicted health care costs and costs for home care in one-year horizon for women, 65 years, married/co-living, Danish ethnicity, low education and living in the Capital Region estimated using a generalized estimating equation gamma regression model for repeated measures including sex, age, marital status, ethnicity, education and region as covariates. Because of no convergence in the model material status and ethnicity were omitted estimating costs for home care.

[§]Predicted health care costs and costs for home care in three-year horizon for women, 65 years, married/co-living and low education estimated using a generalized estimating equation gamma regression model for repeated measures including sex, age and education. Because of no convergence in the model age and education were omitted estimating costs for home care.

[&]Surgery is not predicted in a three-year horizon because of no convergence of the model.

Table S4. Mean public transfer payments one year prior to and one or three years following GLA:D for knee and hip patients

	One-year horizon							Three-year horizon						
	Pre-period (1 year)	Post-period (mth 1-3)		Post-period (mth 4-12)		Post-period (1 year)		Pre-period (1 year)	Post-period (year 1)		Post-period (year 2)		Post-period (year 3)	
	Weeks/ month	Weeks/ month	p-value	Weeks/ month	p-value	Weeks/ month	p-value	Weeks/ year	Weeks/ year	p-value	Weeks/ year	p-value	Weeks/ year	p-value
	Knee patients in workforce (n: 5,586)							Knee patients in workforce (n: 905)						
Public transfer payments														
Unemployed	0.26	0.29	0.465	0.30	0.104	0.29	0.148	2.93	3.23	0.996	3.03	1.000	2.91	1.000
Sheltered employment	0.17	0.16	1.000	0.16	1.000	0.16	1.000	1.48	1.52	1.000	1.61	1.000	1.68	0.999
Sick pay	0.14	0.19	0.000	0.16	0.807	0.17	0.159	1.55	1.88	0.830	1.64	1.000	1.24	0.798
Rehabilitation	0.01	0.01	0.998	0.01	1.000	0.01	0.999	0.09	0.03	0.964	0.09	1.000	0.06	1.000
Education	0.01	0.01	1.000	0.01	1.000	0.01	1.000	0.20	0.18	1.000	0.23	1.000	0.20	1.000
Disability pension	0.29	0.30	1.000	0.29	1.000	0.30	1.000	3.51	3.53	1.000	3.20	0.000	2.93	0.939
Early retirement	0.37	0.46	0.001	0.46	0.002	0.46	0.001	5.58	6.73	0.598	6.36	0.907	4.89	0.935
	Hip patients in workforce (n: 1,543)							Hip patients in workforce (n: 264)						
Public transfer payments														
Unemployed	0.22	0.23	1.000	0.24	0.998	0.23	0.999	2.28	2.57	1.000	2.30	1.000	1.80	0.995
Sheltered employment	0.16	0.16	1.000	0.16	1.000	0.16	1.000	1.72	1.72	1.000	1.50	1.000	1.78	1.000
Sick pay	0.10	0.14	0.202	0.16	0.006	0.15	0.009	1.35	1.85	0.963	1.72	0.992	1.48	1.000
Rehabilitation	0.00	0.01	0.996	0.00	1.000	0.00	1.000	0.04	0.06	1.000	0.19	0.986	0.41	0.622
Education	0.01	0.01	1.000	0.01	1.000	0.01	1.000	0.27	0.20	1.000	0.20	1.000	0.12	0.997
Disability pension	0.37	0.37	1.000	0.37	1.000	0.37	1.000	4.34	4.45	1.000	3.98	1.000	3.47	0.991
Early retirement	0.45	0.56	0.128	0.56	0.129	0.56	0.126	7.73	9.78	0.810	8.59	0.999	6.08	0.876

Table S5. Sensitivity analysis - adjusted estimated health care cost per QALY from baseline to 12 months for knee and hip patients attending GLA:D® in private clinics, municipal clinics and patients with complete information

	Knee			Hip		
	Change in health care costs (€) (95 % CI)	Change in EQ-5D (QALY) (95 % CI)	Euro pr. QALY (95 % CI)	Change in health care costs (€) (95 % CI)	Change in EQ-5D (QALY) (95 % CI)	Euro pr. QALY (95 % CI)
Private clinic[§]	267	0.036	7,464	651	0.028	22,914
	(181-385)	(0.033-0.038)	(5,485-10,132)	(398-1,050)	(0.024-0.033)	(16,583-31,818)
Municipal clinic[#]	396	0.032	12,292	443	0.028	15,550
	(118-949)	(0.026-0.039)	(4,538-24,333)	(69-2,056)	(0.017-0.043)	(4,059-47,814)
Complete cases[¤]	167	0.035	4,829	579	0.027	21,067
	(74-310)	(0.032-0.037)	(2,313-8,378)	(284-1,142)	(0.023-0.032)	(12,348-35,388)

All analyses are adjusted for age, gender, marital status, ethnicity, educational level and region

[§]Analysis restricted to patients attending GLA:D® in a private clinic

[#]Analysis restricted to patients attending GLA:D® in a private clinic

[¤]Analysis restricted to patients with complete information on EQ-5D

CHEERS Checklist

CHEERS checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Title, page 1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Abstract, page 2
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Line 75-81
		Present the study question and its relevance for health policy or practice decisions.	Line 88-91
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Line 125 –142
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Line 110-117
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Line 97-102
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Line 97-102

Section/item	Item No	Recommendation	Reported on page No/ line No
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Line 97-102
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	N/A
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Line 97-102;
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Line 183-188
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	-
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	N/A
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Line 146-181
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for	-

Section/item	Item No	Recommendation	Reported on page No/ line No
		valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Line 154-158
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	N/A
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	N/A
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Line 210-219; Line 229-235
Results			
Study parameters	18	Report the values, ranges, references, and if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Line 146-181

Section/item	Item No	Recommendation	Reported on page No/ line No
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Table 3; Table 4; Figure 2; Table S2; Table S3
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	N/A
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	-
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Line 237-241
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Discussion
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and	Line 455-456

Section/item	Item No	Recommendation	Reported on page No/ line No
		reporting of the analysis. Describe other non-monetary sources of support.	
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Line 469-483

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist

BMJ Open

COST-EFFECTIVENESS OF AN 8-WEEK SUPERVISED EDUCATION AND EXERCISE THERAPY PROGRAM FOR KNEE AND HIP OSTEOARTHRITIS: A PRE-POST ANALYSIS OF 16,255 PATIENTS PARTICIPATING IN GOOD LIFE WITH OSTEOARTHRITIS IN DENMARK (GLA:D®)

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COST-EFFECTIVENESS OF AN 8-WEEK SUPERVISED EDUCATION AND EXERCISE THERAPY PROGRAM FOR KNEE AND HIP OSTEOARTHRITIS: A PRE-POST ANALYSIS OF 16,255 PATIENTS PARTICIPATING IN GOOD LIFE WITH OSTEOARTHRITIS IN DENMARK (GLA:D®)

Dorte T. Grønne[1] PT, MSc, Ewa M. Roos[1] PT, PhD, Rikke Ibsen[2] MSc, Jakob Kjellberg[3] PhD, Søren T. Skou[1,4] PT, PhD

[1] Research Unit for Musculoskeletal Function and Physiotherapy, Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, Denmark

[2] I2minds, Aarhus, Denmark

[3] VIVE - The Danish Center for Social Science Research, Copenhagen, Hovedstaden, Denmark

[4] The Research Unit PROgrez, Department of Physiotherapy and Occupational Therapy, Næstved-Slagelse-Ringsted Hospitals, Denmark

Emails:

DTG: dgronne@health.sdu.dk; EMR: eroos@health.sdu.dk ; RI: rikke@i2minds.dk; JK: jakj@vive.dk; STS: stskou@health.sdu.dk

Corresponding author:

Dorte Thalund Grønne; IOB, SDU, Campusvej 55; DK-5230 Odense M; email: dgronne@health.sdu.dk; Telephone: +45 40 77 99 39

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ABSTRACT

Objectives: To evaluate one-year cost-effectiveness of an 8-week supervised education and exercise program delivered in primary care to patients with symptomatic knee or hip osteoarthritis (OA).

Design: A registry-based pre-post study linking patient level data from the Good Life with osteoArthritis in Denmark (GLA:D®) registry to national registries in Denmark.

Setting and participants: 16,255 patients with symptomatic knee or hip OA attending GLA:D®.

Intervention: GLA:D® is a structured supervised patient education and exercise program delivered by certified physiotherapists and implemented in Denmark.

Outcome measures: Adjusted health care costs per Quality-Adjusted Life Year (QALY) gained from baseline to one year (ratio of change in health care costs to change in EQ-5D). All adjusted measures were estimated using a generalized estimating equation gamma regression model for repeated measures. Missing data on EQ-5D were imputed with Multiple Imputations (3 months: 23%; 1 year: 39 %).

Results: Adjusted change in health care cost was 298€ (95% CI: 206-419) and 640€ (95% CI: 400-1,009) and change in EQ-5D was 0.035 (95% CI: 0.033-0.037) and 0.028 (95% CI: 0.025-0.032) for knee and hip patients, respectively. Hence estimated adjusted health care costs per QALY gained was 8,497€ (95% CI: 6,242-11,324) for knee and 22,568€ (95% CI: 16,000-31,531) for hip patients. In patients with high compliance, the adjusted health care costs per QALY gained was 5,438€ (95% CI: 2,758-9,231) for knee and 17,330€ (95% CI: 10,041-29,364) for hip patients. Health care costs per QALY were below conventional thresholds for willingness-to-pay at 22,804€

(20,000£) and 43,979€ (50,000 USD), except the upper limit of the 95% CI for hip patients which was in between the two thresholds.

Conclusions: A structured 8-week supervised education and exercise program delivered in primary care was cost-effective at one year in patients with knee or hip OA supporting large scale implementation in clinical practice.

Keywords: knee, hip, osteoarthritis, exercise therapy, patient education, cost-effectiveness

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The study included a large number of rural and urban patients with knee or hip OA treated in primary care across Denmark.
- All costs reported are real-life costs retrieved on an individual level from a range of high-quality national registries.
- The study is a pre-post study reporting change in health care costs against change in generic health related quality of life (EQ-5D).
- Health care costs per Quality-Adjusted Life Year (QALY) was reported in a one-year horizon and additional change in health care costs were reported in a three-year horizon.
- 23% and 39 % of the patients did not provide data on EQ-5D immediately following the intervention and at one year respectively, and the missing data was imputed with Multiple Imputations.

INTRODUCTION

Knee and hip osteoarthritis (OA) are major contributors to disability and chronic pain worldwide and the implications for both the patients and health care systems are severe,[1,2]. The cost related to OA is estimated to be between 1% and 2.5% of a country's gross domestic product (GDP) in high-income countries,[1], and total annual costs in Europe are estimated to be up to 817 billion € (2013),[3]. The number of people living with OA has increased over the last years and is expected to increase substantially in the future due to an ageing and more overweight and obese population,[4]. This will have extensive societal impact, emphasizing the need for identifying and implementing cost-effective treatment options that can help relieve the pressure health care services are facing around the world,[4].

Clinical guidelines recommend a stepwise treatment approach, including education and exercise therapy as first-line treatment for knee and hip OA,[5-8] with substantial evidence supporting the effects of supervised exercise therapy on pain and physical function,[9-10]. However, studies of quality of care report that exercise therapy is underutilized, estimated to be provided to less than 40% of patients with OA,[11,12]. To support the implementation of clinical guidelines into clinical practice, Good Life with osteoArthritis in Denmark (GLA:D®) was initiated in 2013 and has been implemented across Denmark. The treatment part of GLA:D® is an 8-week supervised patient education and exercise therapy program delivered in primary care for patients with knee or hip OA and has shown positive results on pain, physical function, quality of life (QOL), intake of painkillers and sick leave,[13].

Results from previous evaluations of the cost-effectiveness of first-line treatment including exercise therapy and targeting knee or hip OA are heterogeneous, and little is known about the cost-effectiveness of supervised education and exercise therapy implemented in primary care,[14,15]. Such evaluation is warranted when deciding whether to implement a structured first-line treatment program, and therefore the aim of the study was to evaluate the cost-effectiveness of GLA:D®. We hypothesized that GLA:D® would be cost-effective for both knee and hip OA patients.

METHOD

Study Design

This is a registry-based pre-post study evaluating the cost-effectiveness in a healthcare payer perspective of an 8-week supervised education and exercise therapy program (GLA:D®) for patients with symptomatic knee or hip OA by linking patient level data from the GLA:D® registry to national registries in Denmark. In the primary analysis, we reported health care costs in a healthcare payer perspective per QALY gained in a one-year horizon calculated as the ratio of change in health care costs to change in QOL in the same patients. In addition, as a secondary analysis, mean actual health care costs and costs to home care and public transfer payments were reported in a three-year horizon to assess how costs develop over time in this population of patients with a chronic condition. The study conforms to the CHEERS statement for reporting health economic evaluations and recommendations for reporting cost-effectiveness analyses,[16,17].

Intervention

GLA:D® is a structured treatment program delivered over approximately 8 weeks consisting of two patient education sessions, a session with an expert patient, when available, and of 12 one-hour sessions (delivered twice weekly) of supervised group-based neuromuscular exercise therapy,[18,19]. Treating therapists are physiotherapists certified to deliver the intervention on a 2-day course at the University of Southern Denmark delivered by researchers, clinicians, and a former patient. All therapists were instructed in how to diagnose osteoarthritis and informed about differential diagnosis. Patients are usually referred to the program by their general practitioner or an orthopaedic surgeon, but they may also refer themselves directly. From 2014 to 2016, the GLA:D® program was delivered in 283 private clinics across the country and in 28 municipal rehabilitation centers of 98 municipalities in Denmark. Most of the patients attending the program in private physiotherapy clinics would receive public reimbursement of approximately 40% of the fee and most patients attending municipal rehabilitation centers would not be charged. A detailed description of the GLA:D® program has previously been published,[13].

The GLA:D® registry has previously been approved by the Danish Data Protection Agency (no. 10.084) and according to the local ethics committee of the North Denmark Region, ethics approval of GLA:D® was not needed. According to the Danish Data Protection Act, patient consent was not required as personal data was processed exclusively for research and statistical purposes.

Population

Patients are eligible for the GLA:D® program if they have a clinical diagnosis of knee and/or hip OA as evaluated by the treating physiotherapist i.e. pain or functional limitations associated with knee or hip OA and do not meet any of the following exclusion criteria: 1) another reason for the joint symptoms than OA (e.g. tumor, inflammatory joint disease or patellar tendinopathy), 2) other symptoms that are more pronounced than the OA symptoms (e.g. chronic generalized pain or fibromyalgia), or 3) do not understand Danish. According to international,[20] and Danish,[21] guidelines radiographs are not needed for a clinical diagnosis of OA, and therefore not part of the GLA:D® eligibility criteria. The current study included patients enrolled between February 4, 2014, when collection of the EuroQoL 5-Dimensions 5-Level questionnaire (EQ-5D) was initiated, and December 31, 2016, allowing for one year follow up since information on all costs was available until the end of 2017. Patients with available baseline information on EQ-5D and information on whether a knee or a hip joint was the most affected joint were included in the study. Reporting mean costs in a three-year horizon was restricted to patients entering the program before December 31, 2014, allowing for three-year follow up, and reporting costs for public transfer payments were restricted to patients aged 18 to 63 years both in the pre- and post-intervention period to ensure that they did not turn 65 during the post-period which was the retirement age in Denmark in 2017. To cover living expenses public transfer payments are in Denmark provided to adults under the age of retirement who e.g. are unemployed, have low/no ability to work or are enrolled in education. Please find more information about the Danish health care system elsewhere,[22].

Variables

Data in the GLA:D® registry are collected at baseline, following the intervention (~3 months as the program is implemented in primary care and some variation in follow up time occurs), and at 12 months and includes demographics, a mix of therapist and patient-reported health measures and outcome measures as well as compliance,[13]. Via the Civil Registration number (CPR), which identifies every citizen in Denmark, the GLA:D® registry was linked to national registries from where actual individual level utilization of somatic health care services (including use of primary health care services, secondary health care services, and use of preceptive medication; i.e. excluding use of psychiatric health care services), home care, and public transfer payments were retrieved,[22]. In Denmark home care including practical help and personal care is offered to citizens with low functional level who are unable to manage everyday life on their own. All prices and costs were converted into Euros (€) and reported in present values (2017-level) based on the Danish Consumer Price Index. Costs were given as mean costs per month (one-year horizon) or year (three-year horizon) and public transfer payments were given as full-time weeks (37 h per week) per month (one-year horizon) or per year (three-year horizon).

Costs related to primary health care services, including visits to physiotherapist, chiropractor, general practitioner, and others (e.g. medical specialist, laboratory work, dentist), were obtained from the Danish National Health Insurance Service Registry. Within the primary health care sector in Denmark physiotherapy is delivered both in private clinics and in municipality settings however, costs for interventions delivered in municipal settings were not available and therefore not included in the analysis. Services and admissions related to secondary health care, including total somatic inpatient and outpatient services, were obtained from the Danish National Patient Registry and associated costs were estimated based on the Danish Case Mix System which organize patients with similar diseases and similar expenses into groups that each have annually adjusted tariffs that reflects practice. The Danish National Patient Registry holds information on all inpatient

admissions and outpatient activities, including accident and emergency visits in Danish hospitals. Every contact is coded in a classification system incorporating ICD-10 codes and use of resources in contacts where surgery in the knee or hip occurred were reported separately. Costs for prescriptive medications were obtained from the Danish National Prescription Registry holding information on all prescriptions on medications, including date of purchase, number of packages and the reimbursement paid by public funds. All drugs are classified according to the Anatomical Therapeutic Chemical Classification System (ATC) and painkillers (ATC-codes: N02A, N02B, M01A, M02AA) and other medications were reported separately. Individual level information on number and duration of visits for personal care and practical help, respectively, was retrieved from Statistics Denmark and the average care costs per hour (2017) in Denmark was used to calculate costs. Information on nursing care was not available and therefore not included in the analysis. Information on public transfer payments was retrieved from the Registry for Public Transfers, which holds information on type and hours of public transfer payments and was reported as the number of weeks receiving transfer payment (unemployment, sheltered employment, sick leave, rehabilitation, education, disability pension, early retirement).

Outcome was reported as QALYs gained measured with EQ-5D converted into an index score using time-trade-off based weights from the Danish crosswalk value set (-0.624 to 1; worst to best),[23]. The EQ-5D comprises of five dimensions: Mobility, self-care, usual activities, pain discomfort and anxiety/depression each having five levels of response options from ‘no problems’ to ‘severe problems’,[24]. QALYs combine time lived and QOL into a single index number where ‘1’ corresponds to one year of full health and ‘0’ corresponds to being dead.

Information on the covariates age (continuous), sex (male or female), marital status (married/coliving or single), ethnic background (western [countries in EU, associated countries and the four Anglo-Saxon countries] or not western [other countries]), educational level (primary, secondary, vocational, short-term, bachelor, long-term or unknown) and administrative region (Capital, Zealand, Southern Denmark, Central Denmark or North Denmark) were retrieved from the Danish Civil Registration System. Most affected joint (knee or hip) and information on compliance were therapist-reported and high compliance was defined as patients attending at least 10 supervised exercise sessions. Type of clinic (private or municipal) was retrieved from the GLA:D® registry and whether the patient died during follow up was retrieved from the Danish Civil Registration System.

Statistical analyses

Descriptive statistics for baseline characteristics, average actual and adjusted costs from somatic health care services and home care and average and adjusted weeks receiving public transfer payments one year prior to and one or three years after entering the program, respectively, were reported. To take the potential influence of covariates into account, actual costs and weeks receiving public transfer payments were adjusted using a generalized estimating equation (GEE) gamma regression model for repeated measures. A model for repeated measures was applied as the same patients were included in the pre and post period. Statistically significant difference between costs in the pre- and post-intervention period was assessed using bootstrap t-test.

We estimated health care costs per QALY gained as the ratio of change in actual total health care costs to change in QOL. Change in health care costs was calculated as the mean cost difference between the year prior to and the year after entering the intervention. QALYs gained was calculated as the mean difference between the EQ-5D score at baseline, calculated as 'the area under the curve' taking change over time into account, representing the QOL the year after entering the program (Figure S1, Supplementary Appendix). Data were not normal distributed and changes in costs and EQ-5D were estimated using a GEE gamma regression model for repeated measures.

In the first step change in health care costs and change in QOL were estimated in two different models, where both raw and adjusted analyses were conducted including gender, age, marital status, ethnicity, educational level and region as covariates. In case of no convergence in the model, selected covariates were omitted. In the second step the ratio of change in health care costs to change in QOL were calculated.

There is no official threshold for willingness-to-pay in Denmark and we compared the health care cost per QALY to predefined willingness-to-pay thresholds of a cost-effective treatment defined by the National Institute for Health and Care Excellence (NICE) at 22,804€ (20,000£) per QALY,[25] and the widely used threshold of 43,979€ (50,000 USD) per QALY,[26]. To explore if adherence to the exercise therapy component had an impact on the results, a sub-analysis repeating all analyses restricted to patients with high compliance was conducted. All analyses were reported separately for knee and hip patients.

As previously proposed for cost-effectiveness studies and clinical trials in OA,[27,28] missing values for the EQ-5D index score at follow up were imputed using Multiple Imputations (MI) with chained equations under the assumption of data being missing at random,[29]. Since EQ-5D was not normal distributed, Predictive Mean Matching was applied, and all baseline variables presented in the study and outcome variables of interest were included in the model. In total, 40 datasets were generated, approximately equal to the largest percentages of missing observations for the outcome as recommended,[30].

Since costs for health care services delivered in municipal settings were not available, all analyses were repeated stratified for patients attending GLA:D® in private physiotherapy clinics vs. in municipal rehabilitation centers. To explore the impact of missing data, a sensitivity analysis repeating all analyses restricted to complete cases was conducted and all analyses were repeated excluding patients who died during follow up.

The significance level for all statistical analyses was defined a priori at $p<0.05$. All analyses were performed using the SAS 9.4 (SAS Institute, North Carolina, USA).

RESULTS

12,162 knee patients and 4,093 hip patients were included in the study and follow up data on EQ-5D were available for 77% immediately after treatment and 61% at one year (Figure 1). Patients with complete information had slightly better, but most likely not clinically relevant better health status at baseline compared to patients with incomplete information (Table S1, Supplementary

Appendix). Baseline characteristics are presented in Table 1. Three quarters of the patients were female, median symptom duration was 2 years, almost two thirds reported use of pain medication and 31% and 4% of knee and hip patients, respectively, reported previous surgery in most affected joint. Seven percent and 17% of knee and hip patients, respectively, reported to have had a joint replacement surgery between start intervention and the 12 m follow up measurement.

[Figure 1]

[Table 1]

Adjusted health care costs and costs for home care one year prior to and three years after entering the intervention are presented in Figure 2a-e, adjusted public transfer payments are presented in Table 2 and mean public transfer payments are presented in Table S2, Supplementary Appendix. Additionally, mean and adjusted costs one year prior to and one/three years after entering the intervention respectively are presented in Table S3 and S4, Supplementary Appendix. To take the potential influence of covariates into account, costs are estimated for average patients, i.e. women, 65 years old, married/co-living, ethnic Danish, low educational level and living in the Capital Region. Public transfer payments are estimated for women, 55 years old, married/co-living, ethnic Danish, low educational level and living in the Capital Region since the population was restricted to adults under the age of retirement in this analysis, as public transfer payments target this age group. In the one-year horizon, monthly adjusted health care costs for knee and hip patients were 263€ and 235€ one year prior to the intervention, rising to 331€ and 397€ the year after entering the program (Table S4, Supplementary Appendix). In the three-year horizon, yearly adjusted health care costs one year prior to the intervention were 3,392€ and 3,051€ for knee and hip patients, rising to 4,128€

and 4,473€ the third year after entering the intervention, observing the highest costs the second year post-intervention for knee patients and the first year post-intervention for hip patients (Figure 2a). The increase in mean health care costs was mainly due to costs related to surgeries in the knee or hip which the first year after index date in the adjusted analysis accounted for 46€/month of an increase in costs of 68€/month in knee patients and 130.8€/month of an increase in costs of 162.8€/month in hip patients (Table S4, Supplementary Appendix). On average, the raw EQ-5D score increased from 0.711 to 0.756 points for knee patients and from 0.705 to 0.747 for hip patients from baseline to one year follow up (Table 3).

[Figure 2]

[Table 2]

[Table 3]

Adjusted change in health care cost from the year prior to entering GLA:D® to the year after entering GLA:D® was 298€ (95% CI: 206-419) and 640€ (95% CI: 400-1,009) and QALYs gained were 0.035 (95% CI: 0.033-0.037) and 0.028 (95% CI: 0.025-0.032) for knee and hip patients, respectively. Hence, one-year estimated adjusted health care costs was 8,497€ (95% CI: 6,242-11,324) for knee patients and 22,568€ (95% CI: 16,000-31,531) for hip patients per QALY gained (Table 4). Restricting the regression analysis to patients with high compliance, the one-year adjusted health care costs per QALY gained was lower compared to all patients; 5,438€ (95% CI: 2,758-9,231) for knee patients and 17,330€ (95% CI: 10,041-29,364) for hip patients primarily due to lower change in health care costs (Table 4). Although the upper limit of the 95% CI for hip patients was in between the two predefined willingness-to-pay thresholds, the estimated health care

costs per QALY for both knee and hip patients were below both of the two predefined willingness-to-pay thresholds.

[Table 4]

Sensitivity analyses showed that knee and hip patients attending GLA:D® in a private clinic had similar health care costs per QALY but that patients attending GLA:D® in a municipal setting had higher costs for knee patients and lower costs for hip patients compared to all patients. This difference was primarily explained by different change in health care costs (Table S5, Supplementary Appendix). The complete case analysis showed lower change in health care costs and lower health care costs per QALY for knee patients (4,829€ (95% CI: 2,313-8,378)) but for hip patients the ratio was similar to that of all patients (Table S5, Supplementary Appendix). 53 patients died within the one-year follow up period and 11 of these within the first 3 months. Repeating all analyses excluding deaths in the regression analyses showed results similar to the main analysis (data not shown).

DISCUSSION

Our study demonstrated that an 8-week supervised patient education and exercise therapy program for knee or hip OA implemented in primary care is cost-effective in a one-year horizon with health care costs of 8,497€ per QALY for knee patients and 22,568€ for hip patients who signed up for the

intervention. Despite the physiotherapy visits needed to participate in the GLA:D® program, increased health care costs were primarily related to knee or hip surgeries (accounting for 70 and 80% of the increased costs, respectively) and although the mean absolute change in health related QOL is relatively low (~0.03) the intervention is still considered cost-effective. These results support large scale implementation of GLA:D® in clinical practice.

To our knowledge this is the first study evaluating the cost-effectiveness of a combined supervised OA education and exercise therapy program with widespread implementation in primary care. Previous analyses of the GLA:D® program, but with twice the number of supervised neuromuscular exercise sessions, weight loss, insoles and pain medication if needed, have found similar results,[15,31]. A model-based study suggested that exercise therapy and education was cost-effective as compared to usual care for patients with knee or hip OA in Canada[31], while an analysis of results from a randomized trial comparing supervised exercise therapy, education and other recommended non-surgical interventions to written advice in patients with moderate to severe knee OA found the intervention to be cost-effective with incremental cost effectiveness ratios of 6,229 to 20,688 €/QALY,[15]. Even though our study is a pre-post study and therefore not directly comparable our findings are also in line with other previous studies which have indicated that supervised exercise therapy alone as treatment for OA is cost-effective. Three randomized trials demonstrated that supervised exercise therapy in addition to usual care, supplementary class-based exercise in addition to a home-based program and supervised exercise therapy compared to general practitioner care alone was likely to be cost-effective in people with knee and/or hip OA,[32-34]. Also, a model-based study estimated that adding the combination of diet and exercise therapy to usual care for overweight and obese patients with knee OA was cost-effective,[35]. Our study adds

to this body of evidence, that large-scale implementation in clinical practice of a structured combined supervised education and exercise therapy program seems cost-effective in a one-year horizon.

In this study, the increased health care costs both one and three years after entering the GLA:D® program were primarily related to surgeries in the knee or hip. According to a stepwise treatment approach, joint replacement surgery is considered to be relevant in patients with end-stage OA once all appropriate non-surgical treatment options such as patient education and supervised exercise therapy of sufficient dose and length, weight loss, walking aids and pain medication have failed to reduce symptoms sufficiently,[36,37]. Existing evidence indicates that providing supervised exercise therapy can have positive impact on the number of patients having joint replacement surgery,[38-40], time to surgery,[39,40] and outcomes from surgery[41]. Ackerman et al conducted a budget impact analysis of implementing a first-line management program such as GLA:D® in Australia and demonstrated that if total knee replacement was avoided in only 1 in 12 GLA:D® participants, the program would generate cost savings in the Australian health care system,[42]. Although the lack of control group in the current study precludes analyses of avoidance of joint replacements, it highlights that regardless of surgery during follow up, supervised education and exercise therapy is cost-effective.

As a result of similar change in EQ-5D, but lower change in health care costs, health care costs per QALY were lower in patients compliant to the intervention (i.e. attending at least 10 supervised exercise sessions) compared to all patients enrolled in the program, indicating that the dosage of exercise therapy is important. Although we did not find that higher compliance was associated with

greater effects on the EQ-5D, the lower change in health care costs in the compliant patients underlines the importance of exercise dosage as suggested by a systematic review and meta-regression analysis of 48 randomized controlled trials in patients with knee OA showing that 12 or more supervised exercise sessions are more effective than fewer supervised sessions,[43], and a systematic review and meta-analysis in patients with hip OA showing that supervised exercise therapy with high compliance with dose recommendations compared to uncertain compliance (studies where compliance was not possible to categorize according to recommendations) was more effective,[44]. Although dosage seems important for the effect and cost-effectiveness, knowledge of optimal exercise dosage in OA is still lacking,[9,43,45].

As there is no official threshold defining a cost-effective treatment in Denmark, we compared the health care costs per QALY to two different internationally widely used willingness-to-pay thresholds. Although the estimated health care costs per QALY for both knee and hip patients were below both of the two thresholds, the upper limit of the 95% CI for hip patients was in between the two thresholds, thus we cannot rule out that the true health care costs per QALY for hip patients is above the lower willingness-to-pay threshold (22,804€). A threshold value for willingness-to-pay for improvements in health is arbitrary and depending on the context such as budget and other treatment options,[26]. Country-level threshold value based on GDP per capita has been discussed but remains unsettled,[46]. When deciding which treatment options to implement and offer, the results from this study can support clinicians and decision-makers in terms of one-year cost-effectiveness of supervised education and exercise therapy implemented nationwide for patients with knee and hip OA in clinical practice.

Strengths and limitations

The major strength of the study is that all costs reported are real-life costs retrieved on an individual level from a range of high-quality national registries supporting the reliability and validity of the costs,[22,47,48]. Even though it is likely that a higher level of heterogeneity in treatment protocols occurred compared to in rigorous clinical trials, another major strength is that the study included a large number of rural and urban patients with wide inclusion criteria; joint pain and functional limitations associated with OA, retrieved from a nationwide registry supporting the generalizability of the findings.

The main limitation of the study is that the study is a pre-post study where change in health care costs was evaluated against change in EQ-5D. Without a proper control group, it cannot be ruled out that the observed change in EQ-5D is related to other factors than the treatment such as placebo or regression to the mean. In the analysis EQ-5D measured at baseline represented the QOL the year prior to the intervention, but there is a risk that the change in QOL were overestimated as patients often seek treatment at time of worsening of symptoms. Also, change in costs can potentially have been affected by increasing age, since health care costs are expected to increase with increased age and accompanied morbidity,[49]. As a consequence of lack of model convergence marital status and ethnicity was omitted as covariates in the adjusted model evaluating the costs for home care estimating change in costs per QALY gained in a one-year horizon. As costs related to home care comprises a rather small proportion of the total costs it is not considered to affect the main result.

In the current study, health care costs per QALY was evaluated in a one-year horizon and additionally change in costs were reported in a three-year horizon. OA is a long-term chronic condition,[36], thus evaluating cost-effectiveness in a one-year horizon is a relatively short time horizon warranting further long-term cost-effective analyses. However, a recent model-based cost-effectiveness analysis suggested that a physical activity program for patients with knee OA would lead to favorable long-term clinical and economic benefits,[50].

Only around 60% of the costs covering the program for most patients attending GLA:D® in private physiotherapy clinics were taken into account in the analyses i.e. patients out-of-pocket costs and costs covering the program in municipal settings as well as medications bought over the counter were not included. As the increase in costs in the primary health care sector and in costs covering medications the first year following index date only constitute a very low proportion of the increased costs in total, this limitation is not considered to substantially affect the overall results.

There was a loss to follow up in the GLA:D® registry and conducting a sensitivity analysis restricted to patients with complete information revealed that they had less mean change in health care costs than all included patients, indicating a risk of selective loss to follow up in the GLA:D® registry, however, the evaluation on health care costs per QALY included all patients enrolled in GLA:D®, imputing the missing outcome values at follow up. Imputing missing outcome values relied on the assumption that data were missing at random, i.e. the missingness was related to variables included in the model. However, there is a risk that loss to follow up was related to unobserved factors not available for the analysis (e.g. good or bad outcome from the GLA:D® program). One third did not provide information on compliance and there is a risk that lower change

in health care costs in the sub-group of patients with high compliance is affected by selection bias i.e. that the lower change in health care costs could be due to systematically differences in the use of health care services between those providing and not providing information about compliance rather than due to the intervention. However, we did not find clinically relevant health status differences at baseline among those not providing information on compliance compared to those who provided this information (data not shown).

The current study is based on real-world outcome data collected in nationwide physiotherapy clinics and actual health care costs retrieved from national registries, supporting the generalizability of the results. However, patients attending GLA:D® are a preselected group of patients who are commonly referred to physiotherapy for their symptoms with most being able to pay partly for the intervention, which might limit the generalizability.

CONCLUSIONS

A structured 8-week supervised education and exercise therapy program delivered in physiotherapy practice was cost-effective at one year in patients with knee and hip OA compared to conventional willingness-to-pay thresholds except the upper limit of the 95% CI for hip patients which was in between two thresholds. Both health-related QOL and health care costs increased during the one-year time horizon, the latter mainly due to knee or hip surgeries. The results support large scale implementation of a structured supervised evidence-based patient education and exercise therapy program targeting patients with knee or hip OA and can guide clinicians and decision makers on what to expect when such programs are implemented in clinical practice.

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PATIENT AND PUBLIC INVOLVEMENT STATEMENT

Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

DATA SHARING STATEMENT

The data from the national Danish registries used in this study is available from Statistics Denmark. However, restrictions apply to the availability, as the data was used under license for the current study, and so are not publicly available. Data are however available from the authors ER and STS upon reasonable request and with permission of Statistics Denmark.

AUTHOR CONTRIBUTIONS

Study conception and design: DTG, ER, RI, JK, STS

Acquisition of data: DTG, ER, STS

Analysis and interpretation of data: DTG, ER, RI, JK, STS

Drafting the article: DTG, STS

Revising the article critically for important intellectual content: DTG, ER, RI, JK, STS

Final approval of the article: DTG, ER, RI, JK, STS

Obtaining of funding: STS

ROLE OF THE FUNDING SOURCE

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CONFLICT OF INTEREST

Dr. Roos is deputy editor of Osteoarthritis and Cartilage, the developer of the Knee injury and Osteoarthritis Outcome Score (KOOS) and several other freely available patient-reported outcome measures and co-founder of Good Life with osteoArthritis in Denmark (GLA:D®), a not-for profit initiative hosted at University of Southern Denmark aimed at implementing clinical guidelines for osteoarthritis in clinical practice.

Dr. Skou is associate editor of the Journal of Orthopaedic & Sports Physical Therapy, has received grants from The Lundbeck Foundation, personal fees from Munksgaard, all of which are outside the submitted work. He is co-founder of GLA:D®.

R Ibsen: None

J Kjellberg: None

Dr. Grønne is employed as data manager in the GLA:D® project.

Ethics Statement

As the study is a registry-based study, according to Danish legislation ethical approval is not needed and according to the local ethics committee of the North Denmark Region, ethics approval of GLA:D® was not needed.

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TABLE LEGENDS

Table 1. Baseline characteristics in knee and hip patients attending GLA:D®

Table 2. Adjusted public transfer payments one year prior to and one or three years following GLA:D® for knee and hip patients

Table 3. Change in health-related quality of life from baseline to 12 months for knee and hip patients attending GLA:D®

Table 4. Adjusted and raw estimated health care costs per QALY from baseline to 12 months for all knee and hip patients attending GLA:D® and for knee and hip patients with high compliance

Table 1. Baseline characteristics in knee and hip patients attending GLA:D®

	Knee (n: 12,162)	Hip (n: 4,093)
Age (years), mean (SD)	64.1 (9.8)	65.7 (9.4)
Gender (Female), % (n)	73.1 (8,887)	73.6 (3,014)
BMI (kg/m^2), mean (SD)	28.6 (5.3)	26.9 (4.6)
Marital status, % (n)		
Married or living with others	72.4 (8,803)	70.7 (1,079)
Single	27.6 (3,359)	29.3 (1,200)
Ethnic background, % (n)		
Danish	96,2 (11,701)	96.8 (3,961)
Other western	2.5 (299)	2.6 (106)
Not western	1.3 (160)	0.6 (25)
Educational level, % (n)		
Primary	18.7 (2,277)	19.7 (1,493)
Secondary	3.0 (367)	2.7 (112)
Vocational	39.1 (4,761)	36.2 (1,481)
Short-term	4.6 (558)	4.5 (185)
Bachelor	26.2 (3,186)	28.0 (1,145)
Long-term	7.2 (873)	8.0 (329)
Unknown	1.2 (140)	0.9 (35)
Social status, % (n)		
Employed	43.3 (5,264)	36.5 (1,493)
Unemployed	2.1 (256)	1.5 (61)
Sick pay (public funded)	0.7 (86)	0.4 (15)
Disability pension	3.7 (444)	3.7 (152)
Early retirement	6.3 (766)	7.3 (297)
Age pension	42.8 (5,209)	49.5 (2,028)
Other	1.1 (137)	1.1 (47)
Administrative region, % (n)		
Capital Region	27.7 (3,367)	27.6 (1,131)
Region Zealand	13.0 (1,578)	13.1 (535)
Region of Southern Denmark	21.8 (2,654)	25.2 (1,030)
Central Denmark Region	25.4 (3,085)	24.9 (1,021)
North Denmark Region	12.2 (1,478)	9.2 (376)
Number of comorbidities[%], % (n)		
0	38.2 (4,367)	39.7 (1,533)
1	35.7 (4,076)	35.1 (1,358)
2	17.3 (1,979)	16.8 (649)
3 or more	8.8 (1.006)	8.4 (326)
Symptom duration (months), median (IQR)	24 (7-60)	24 (8-48)
Pain intensity (VAS 0-100, best to worst), mean (SD)	48.6 (22.0)	47.6 (21.7)
Bilateral symptoms, % (n)	46.3 (5,614)	26.1 (1,064)
Walk speed[#] (m/sec), mean (SD)	1.49 (0.33)	1.49 (0.34)
Previous surgery in worst joint[&], % (n)	30.7 (3,725)	4.0 (161)
Use of pain medication[¤] (yes), % (n)		
Overall	61.3 (7,431)	64.2 (2,629)
Paracetamol	49.9 (6,073)	53.3 (2,184)
NSAIDs	35.6 (4,325)	34.6 (1,419)
Opioids	7.1 (868)	9.0 (367)
KOOS/HOOS QOL[*] (0-100, best to worst), mean (SD)	45.2 (14.7)	47.4 (15.1)

Missing values: BMI n: 5 (knee), n: 7 (hip); Number of comorbidities n: 711 (knee), n: 215 (hip); Symptom duration (mainly missing due to technical problems): n: 3.157 (knee), n: 1,096 (hip) ; Pain intensity: n:23 (knee), n:9 (hip) ; Bilateral symptoms: n:32 (knee), n:20 (hip) ; Walk speed: n:610 (knee), n:221 (hip); KOOS/HOOS QOL: n: 36 (knee),

n: 21 (hip).

[#]Walking speed was assessed with the 40 m Fast-paces Walk Test under instruction of the GLA:D®-therapist

[¤]Self-reported use of pain medication during last 3 months

[%]Number of comorbidities calculated from self-report of the following conditions: hypertension, cardiovascular diseases, lung diseases, diabetes, stomach diseases, liver- or kidney diseases, blood diseases, cancer, depression, rheumatoid arthritis, neurological disorders, other medical diseases

[&]Self-reported previous surgery in worst joint

[*]Knee injury and Osteoarthritis Outcome Score or Hip disability or Osteoarthritis Outcome Score Quality Of Life sub-scale score

Table 2. Adjusted public transfer payments one year prior to and one or three years following GLAD® for knee and hip patients

	One-year horizon							Three-year horizon						
	Pre-period (1 year)	Post-period (mth 1-3)		Post-period (mth 4-12)		Post-period (year 1)		Pre-period (1 year)	Post-period (year 1)		Post-period (year 2)		Post-period (year 3)	
	Weeks/ month	Weeks/ month	p-value	Weeks/ month	p-value	Weeks/ month	p-value	Weeks/ year	Weeks/ year	p-value	Weeks/ year	p-value	Weeks/ year	p-value
	Knee patients in workforce (n: 5,586)							Knee patients in workforce (n: 905)						
Public transfer payments[#]														
Unemployed	0.24	0.26	0.000	0.27	0.001	0.27	0.000	3.50	3.82	0.314	3.51	0.986	3.32	0.703
Sheltered employment	0.10	0.10	0.959	0.10	0.967	0.10	0.982	1.61	1.59	0.917	1.69	0.671	1.78	0.422
Sick pay	0.13	0.16	0.000	0.14	0.164	0.15	0.029	1.47	1.70	0.295	1.54	0.789	1.16	0.201
Rehabilitation	0.01	0.01	0.254	0.01	0.494	0.01	0.407	0.09	0.03	0.017	0.09	0.960	0.06	0.731
Education	0.01	0.00	0.136	0.01	0.950	0.00	0.770	0.20	0.18	0.907	0.23	0.690	0.20	0.991
Disability pension	0.23	0.24	0.006	0.23	0.259	0.24	0.136	6.02	6.02	0.989	5.91	0.467	6.00	0.966
Early retirement	0.37	0.46	0.000	0.46	0.000	0.46	0.000	6.06	7.35	0.000	7.02	0.071	5.44	0.354
	Hip patients in workforce (n: 1,543)							Hip patients in workforce (n: 264)						
Public transfer payments[§]														
Unemployed	0.19	0.19	0.540	0.20	0.309	0.20	0.325	3.36	3.56	0.730	3.20	0.865	2.90	0.672
Sheltered employment	0.10	0.10	0.458	0.10	0.516	0.10	0.470	1.92	1.80	0.712	1.50	0.217	1.73	0.661
Sick pay	0.10	0.13	0.082	0.16	0.001	0.15	0.003	1.38	2.00	0.127	1.41	0.967	1.32	0.903
Rehabilitation	0.00	0.01	0.202	0.00	0.407	0.00	0.812	0.04	0.06	0.000	0.19	0.000	0.41	0.000
Education	0.01	0.01	0.321	0.01	0.659	0.01	0.557	0.27	0.20	0.393	0.20	0.598	0.12	0.183
Disability pension	0.29	0.26	0.264	0.27	0.502	0.27	0.427	3.81	3.92	0.501	3.66	0.673	3.29	0.171
Early retirement	0.47	0.59	0.000	0.58	0.000	0.58	0.000	9.02	11.54	0.000	10.01	0.422	7.11	0.219

[#]Adjusted weeks receiving public transfer payments in one-year horizon for women, 55 years, married/co-living, Danish ethnicity, low education and living in the Capital Region estimated using a generalized estimating equation gamma regression model for repeated measures including sex, age, marital status, ethnicity, education and region as covariates. Because of no convergence in the model following covariates were omitted: 'Early retirement': sex, marital status, ethnicity, education and region; 'Rehabilitation': age, marital status, ethnicity and education; 'Education': age, marital status, ethnicity and education. Adjusted weeks receiving public transfer payments in three-year horizon for women, 55 years and low education estimated using a generalized estimating equation gamma regression model for repeated measures including sex, age and education as covariates. Because of no convergence in the model following covariates were omitted: 'Sheltered employment': sex and education; Disability pension'': sex and education; 'Early retirement': age.

[§]Adjusted weeks receiving public transfer payments in one-year horizon for women, 55 years, married/co-living, Danish ethnicity, low education and living in the Capital Region estimated using a generalized estimating equation gamma regression model for repeated measures including sex, age, marital status, ethnicity, education and region as covariates. Because of no convergence in the model following covariates were omitted: 'Early retirement': sex, marital status, ethnicity, education and region; 'Rehabilitation': age, marital status, ethnicity, education and region; 'Education': age, marital status, ethnicity, education and region. Adjusted weeks receiving public transfer payments in three-year horizon for women, 55 years and low education estimated using a generalized estimating equation gamma regression model for repeated measures including sex, age and education as covariates. Because of no convergence in the model following covariates were omitted:

731 ‘Sheltered employment’: sex and education; Disability pension’’: sex and education; ‘Early retirement’: age; ‘Rehabilitation’: sex, age and education; ‘Rehabilitation:
732 sex, age and education.

Table 3. Change in health-related quality of life from baseline to 12 months for knee and hip patients attending GLA:D®

	Knee (n: 12,162)				Hip (n: 4,093)			
	Pre period QALY (Baseline EQ-5D)	**3 months EQ-5D§**	**12 months EQ-5D§**	**Composite post period QALY#**	**Pre period QALY** (Baseline EQ-5D)	**3 months EQ-5D§**	**12 months EQ-5D§**	**Composite post period QALY#**
Mean	0.711	0.752	0.756	0.748	0.705	0.733	0.747	0.735
SD	0.113	0.121	0.134	0.107	0.110	0.127	0.144	0.108

§Missing observations for EQ-5D at 3 and 12 months were imputed by Multiple Imputations

#One year post period QALY was calculated as the area under the curve taking both 3- and 12-months measurements into account

Table 4. Adjusted and raw estimated health care costs per QALY from baseline to 12 months for all knee and hip patients attending GLA:D® and for knee and hip patients with high compliance

	Knee			Hip		
	Change in health care costs (€) (95 % CI)	**Change in EQ-5D (QALYs) (95 % CI)§**	**Euro pr. QALY (95 % CI)§**	**Change in health care costs (€) (95 % CI)**	**Change in EQ-5D (QALYs) (95 % CI)§**	**Euro pr. QALY (95 % CI)§**
Adjusted#	298 (206-419)	0.035 (0.033-0.037)	8,497 (6,242–11,324)	640 (400-1,009)	0.028 (0.025-0.032)	22,568 (16,000-31,531)
Unadjusted	895 (719-1,088)	0.037	24,236	2,162 (1,723-2,671)	0.030	71,478
High compliance#,¤	197 (91-360)	0.036 (0.033-0.039)	5,438 (2,758-9,231)	492 (241-969)	0.028 (0.024-0.033)	17,330 (10,041-29,364)

§Confidence Interval not generated from the MI

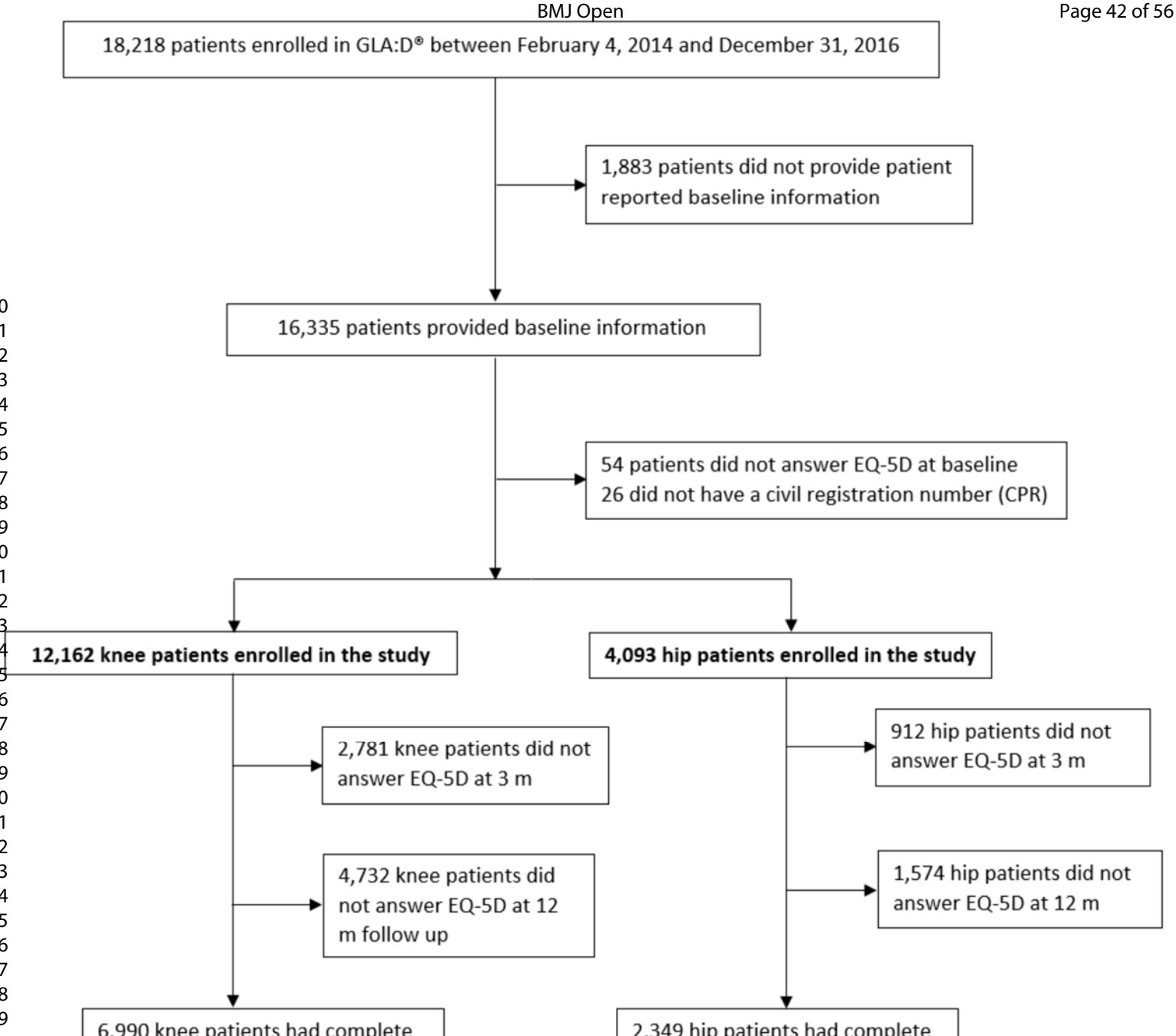
#Adjusted for age, gender, marital status, ethnicity, educational level and region

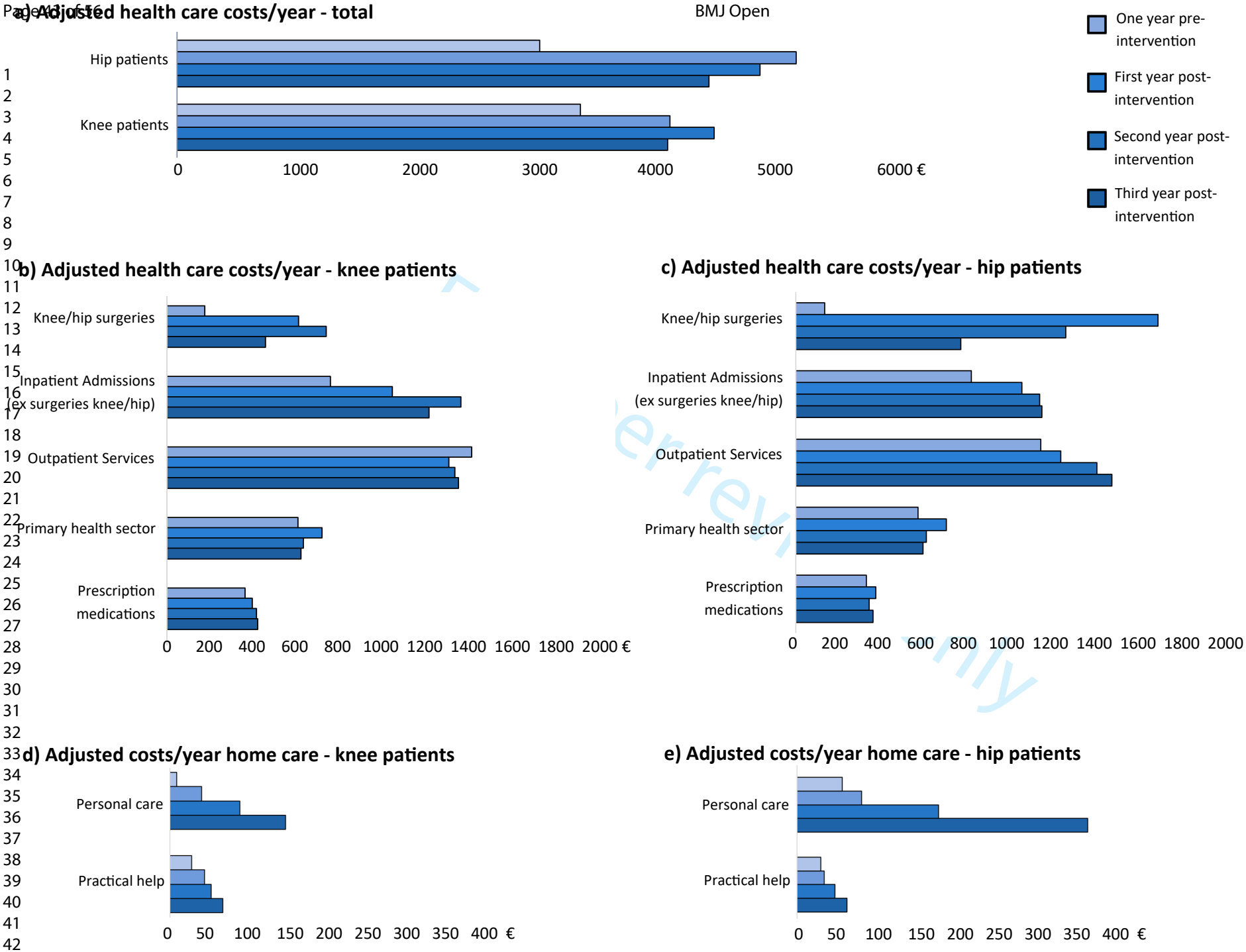
¤High compliance group defined as patients attending minimum 10 supervised exercise sessions

FIGURE LEGENDS

Figure 1. Flow chart

Figure 2. Adjusted healthcare costs and home care costs one year prior to and up to three years following GLA:D® for knee and hip patients


18,218 patients enrolled in GLA:D® between February 4, 2014 and December 31, 2016
1,883 patients did not provide patient reported baseline information
16,335 patients provided baseline information
54 patients did not answer EQ-5D at baseline
26 did not have a civil registration number (CPR)
12,162 knee patients enrolled in the study
4,093 hip patients enrolled in the study
2,781 knee patients did not answer EQ-5D at 3 m
912 hip patients did not answer EQ-5D at 3 m
4,732 knee patients did not answer EQ-5D at 12 m follow up
1,574 hip patients did not answer EQ-5D at 12 m
6,990 knee patients had complete information on EQ-5D
2,349 hip patients had complete information on EQ-5D



Adjusted health care costs and costs for home care in three-year horizon for women, 65 years, married/co-living and low education estimated using a generalized estimating equation gamma regression model for repeated measures including sex, age, and education. Because of no convergence in the model age and education were omitted estimating costs for home care.

Supplementary Appendix

Figure S1: Illustration of how quality of life was calculated the year pre- and post-intervention

Table S1: Baseline characteristics in patients with complete information and patients with loss to follow up

Table S2: Mean public transfer payments one year prior to and one or three years following GLA:D® for knee and hip patients

Table S3: Mean health care costs and home care costs one year prior to and one or three years following GLA:D® for knee and hip patients

Table S4: Adjusted health care costs and home care costs one year prior to and one or three years following GLA:D® for knee and hip patients

Table S5. Sensitivity analysis - adjusted estimated health care cost per QALY from baseline to 12 months for knee and hip patients attending GLA:D® in private clinics, municipal clinics and patients with complete information

Figure S1: Illustration of how quality of life was calculated the year pre and post intervention

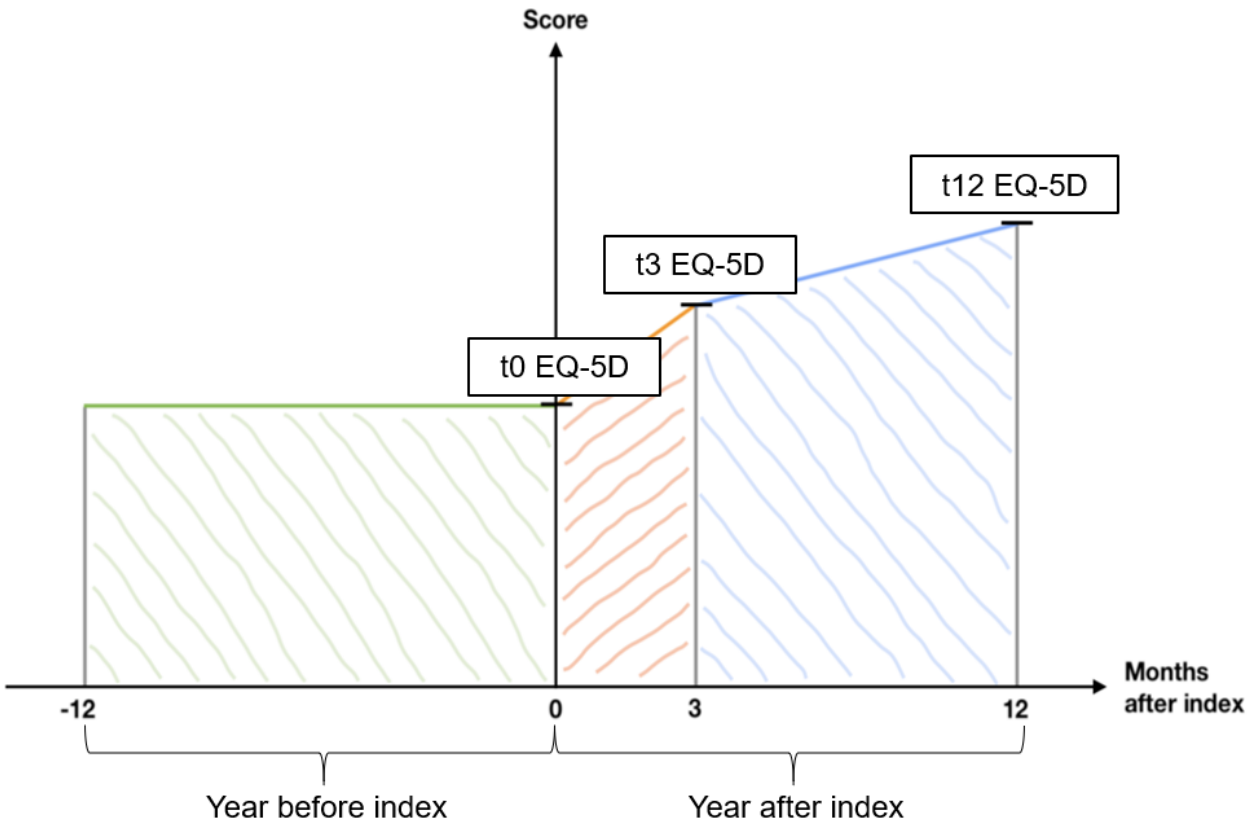


Table S1: Baseline characteristics in patients with complete information and patients who had incomplete information

	Complete information		Incomplete information	
	Knee (n: 6,990)	Hip (n: 2,349)	Knee (n: 5,173)	Hip (n: 1,749)
Age (years), mean (SD)	64.4 (9.1)	65.7 (8.7)	63.7 (10.7)	65.7 (10.3)
Gender (Female), % (n)	73.2 (5,113)	74.6 (1,753)	73.0 (3,777)	72.2 (1,263)
BMI (kg/m^2), mean (SD)	28.4 (5.2)	26.6 (4.4)	28.9 (5.4)	27.2 (4.9)
Marital status, % (n)				
Married or living with others	75 (5,256)	73 (1,714)	69 (3,547)	68 (1,179)
Single	25 (1,730)	27 (634)	31 (1,629)	32 (566)
Ethnic background, % (n)				
Danish	97 (6,773)	97 (2,276)	95 (4,928)	97 (1,685)
Other western	2 (160)	3 (60)	3 (139)	3 (46)
Not western	1 (53)	0.5 (11)	2 (107)	0.8 (14)
Educational level, % (n)				
Primary	17 (1,177)	18 (420)	21 (1,100)	22 (386)
Secondary	3 (197)	3 (69)	3 (170)	2 (43)
Vocational	38 (2,671)	34 (792)	40 (2,090)	39 (689)
Short-term	5 (322)	5 (123)	5 (236)	4 (62)
Bachelor	28 (1,999)	31 (722)	31 (1,187)	24 (423)
Long-term	8 (546)	9 (200)	9 (327)	7 (129)
Unknown	1 (74)	1 (22)	1 (66)	1 (13)
Social status, % (n)				
Employed	44 (3,012)	37 (866)	44 (2,252)	37 (627)
Unemployed	0.5 (35)	0.3 (6)	0.8 (42)	0.4 (7)
Sick pay (public funded)	0.5 (37)	0.4 (9)	1 (49)	0.3 (6)
Disability pension	3 (228)	3 (76)	4 (216)	4 (76)
Early retirement	8 (527)	9 (2025)	5 (239)	6 (95)
Age pension	43 (3,006)	49 (1,137)	43 (2,203)	52 (891)
Other	1 (69)	1 (33)	1 (68)	0.8 (14)
Sick leave[!], % (n)	4.9 (314)	3.2 (77)	6.8 (353)	3.8 (67)
Administrative region, % (n)				
Capital Region	27 (1,875)	26 (606)	29 (1,492)	30 (525)
Region Zealand	13 (936)	14 (327)	12 (642)	12 (208)
Region of Southern Denmark	23 (1,579)	26 (602)	21 (1,075)	25 (428)
Central Denmark Region	26 (1,796)	26 (609)	25 (1,275)	24 (412)
North Denmark Region	11 (800)	9 (204)	13 (1,289)	10 (172)
Number of comorbidities[%], % (n)				
0	39.2 (2,575)	41.9 (928)	36.9 (1,798)	36.5 (608)
1	36.2 (2,381)	35.5 (787)	35.0 (1,704)	34.7 (578)
2	17.0 (1,118)	15.8 (350)	17.8 (867)	18.1 (302)
3 or more	7.7 (504)	6.9 (152)678	10.4 (505)	10.7 (178)
Symptom duration (months), median (IQR)	24 (7-60)	24 (8-48)	24 (7-60)	24 (8-48)
Pain intensity (VAS 0-100, best to worst), mean (SD)	47.3 (21.8)	45.9 (21.4)	50.3 (22.3)	49.7 (22.0)
Bilateral symptoms, % (n)	46.7 (3,259)	26.6 (622)	45.7 (2,355)	25.4 (442)
Walk speed[#] (m/sec), mean (SD)	1.51 (0.32)	1.52 (0.33)	1.46 (0.35)	1.45 (0.35)

Previous surgery in worst joint[&], % (n)	30.2 (2,112)	3.2 (78)	31.3 (1,619)	4.8 (84)
Receive home care, % (n)	8.9 (621)	9.6 (224)	11.5 (593)	12.4 (215)
Use of pain medication[¤] (yes), % (n)				
Overall	60.9 (4,256)	62.7 (1,473)	61.8 (3,196)	66.1 (1,156)
Paracetamol	49,5 (3,463)	52.9 (1,243)	50.5 (2,610)	53.8 (941)
NSAIDs	35.8 (2,504)	32.5 (764)	35,2 (1,1821)	37.5 (655)
Opioids	6.6 (459)	8.1 (190)	7.9 (409)	10.1 (177)
KOOS/HOOS QOL[*] (0-100, best to worst), mean (SD)	46.0 (14.5)	47.9 (15.0)	44.1 (15.0)	46.7 (15.3)

Missing values: BMI: n: 2 (knee, complete), n: 5 (hip, complete), n: 3 (knee, incomplete), n: 2 (hip, incomplete); Ethnic background: n: 1 (hip, complete), n: 2 (knee, incomplete); Social status: n: 72 (knee, complete), n: 19 (hip, complete), n: 107 (knee, incomplete), n: 29 (hip, incomplete); Sick leave: n: 6 (knee, complete), n: 1 (hip, complete), n: 19 (knee, incomplete), n: 3 (hip, incomplete); Number of comorbidities: n: 412 (knee, complete), n: 132 (hip, complete), n: 299 (knee, incomplete), n: 83 (hip, incomplete); Symptom duration (mainly missing due to technical problems): n: 1.730 (knee, complete), n: 595 (hip, complete), n: 1.427 (knee, incomplete), n: 501 (hip, incomplete); Pain intensity: n: 8 (knee, complete), n: 3 (hip, complete), n: 15 (knee, incomplete), n: 6 (hip, incomplete); Bilateral symptoms: n: 14 (knee, complete), n: 10 (hip, complete), n: 18 (knee, incomplete), n: 10 (hip, incomplete); Walk speed: n: 309 (knee, complete), n: 100 (hip, complete), n: 301 (knee, incomplete), n: 121 (hip, incomplete); Receive home care: n: 31 (knee, complete), n: 8 (hip, complete), n: 36 (knee, incomplete), n: 8 (hip, incomplete); KOOS/HOOS QOL: n: 17 (knee, complete), n: 9 (hip, complete), n: 19 (knee, incomplete), n: 10 (hip, incomplete).

[#]Walking speed was assessed with the 40 m Fast-paces Walk Test under instruction of the GLA:D®-therapist

[¤]Self-reported use of pain medication during last 3 months

[!]Self-reported sick leave for more than 1 month during last year due to knee/hip

[%]Number of comorbidities calculated from self-report of the following conditions: hypertension, cardiovascular diseases, lung diseases, diabetes, stomach diseases, liver- or kidney diseases, blood diseases, cancer, depression, rheumatoid arthritis, neurological disorders, other medical diseases

[&]Self-reported previous surgery in worst joint

[*]Knee injury and Osteoarthritis Outcome Score or Hip disability or Osteoarthritis Outcome Score Quality Of Life sub-scale score

Table S2. Mean public transfer payments one year prior to and one or three years following GLA:D® for knee and hip patients

	One-year horizon							Three-year horizon						
	Pre-period (1 year)	Post-period (mth 1-3)		Post-period (mth 4-12)		Post-period (1 year)		Pre-period (1 year)	Post-period (year 1)		Post-period (year 2)		Post-period (year 3)	
	Weeks/ month	Weeks/ month	p-value	Weeks/ month	p-value	Weeks/ month	p-value	Weeks/ year	Weeks/ year	p-value	Weeks/ year	p-value	Weeks/ year	p-value
	Knee patients in workforce (n: 5,586)							Knee patients in workforce (n: 905)						
Public transfer payments														
Unemployed	0.26	0.29	0.465	0.30	0.104	0.29	0.148	2.93	3.23	0.996	3.03	1.000	2.91	1.000
Sheltered employment	0.17	0.16	1.000	0.16	1.000	0.16	1.000	1.48	1.52	1.000	1.61	1.000	1.68	0.999
Sick pay	0.14	0.19	0.000	0.16	0.807	0.17	0.159	1.55	1.88	0.830	1.64	1.000	1.24	0.798
Rehabilitation	0.01	0.01	0.998	0.01	1.000	0.01	0.999	0.09	0.03	0.964	0.09	1.000	0.06	1.000
Education	0.01	0.01	1.000	0.01	1.000	0.01	1.000	0.20	0.18	1.000	0.23	1.000	0.20	1.000
Disability pension	0.29	0.30	1.000	0.29	1.000	0.30	1.000	3.51	3.53	1.000	3.20	0.000	2.93	0.939
Early retirement	0.37	0.46	0.001	0.46	0.002	0.46	0.001	5.58	6.73	0.598	6.36	0.907	4.89	0.935
	Hip patients in workforce (n: 1,543)							Hip patients in workforce (n: 264)						
Public transfer payments														
Unemployed	0.22	0.23	1.000	0.24	0.998	0.23	0.999	2.28	2.57	1.000	2.30	1.000	1.80	0.995
Sheltered employment	0.16	0.16	1.000	0.16	1.000	0.16	1.000	1.72	1.72	1.000	1.50	1.000	1.78	1.000
Sick pay	0.10	0.14	0.202	0.16	0.006	0.15	0.009	1.35	1.85	0.963	1.72	0.992	1.48	1.000
Rehabilitation	0.00	0.01	0.996	0.00	1.000	0.00	1.000	0.04	0.06	1.000	0.19	0.986	0.41	0.622
Education	0.01	0.01	1.000	0.01	1.000	0.01	1.000	0.27	0.20	1.000	0.20	1.000	0.12	0.997
Disability pension	0.37	0.37	1.000	0.37	1.000	0.37	1.000	4.34	4.45	1.000	3.98	1.000	3.47	0.991
Early retirement	0.45	0.56	0.128	0.56	0.129	0.56	0.126	7.73	9.78	0.810	8.59	0.999	6.08	0.876

Table S3. Mean health care costs and home care costs one year prior to and one or three years following GLAD® for knee and hip patients

	Pre-period (1 year)	Post-period (mth 1-3)		Post-period (mth 4-12)		Post-period (1 year)		Pre-period (1 year)	Post-period (year 1)		Post-period (year 2)		Post-period (year 3)	
	Cost (€/month)	Cost (€/month)	p-value	Cost (€/month)	p-value	Cost (€/month)	p-value	Cost (€/Year)	Cost (€/year)	p-value	Cost (€/year)	p-value	Cost (€/year)	p-value
	Knee (n: 12,162)							Knee (n: 1,879)						
Health costs (somatic)														
Inpatient Admissions total	**73.1**	**67.7**	0.999	**170.6**	0.000	**144.8**	0.000	**962.1**	**1,785.3**	0.000	**2,086.1**	0.000	**1,729.7**	0.000
Thereof inpatient														
Surgery knee/hip	9.6	17.9	0.004	67.7	0.000	55.2	0.000	160.0	618.4	0.000	681.6	0.000	428.7	0.000
Surgery other	11.3	4.9	0.000	14.1	0.596	11.8	1.000	151.3	225.5	0.866	198.8	0.995	290.1	1.000
Outpatient Services total	**108.4**	**90.3**	0.000	**107.4**	1.000	**103.1**	0.764	**1,421.0**	**1,345.1**	1.000	**1,359.0**	1.000	**1,372.1**	0.771
Thereof outpatient														
Surgery knee/hip	4.3	1.2	0.000	1.7	0.000	1.6	0.000	74.9	16.9	0.000	10.0	0.000	6.0	0.000
Surgery other	1.9	1.8	1.000	1.8	1.000	1.8	1.000	23.4	15.5	0.998	24.4	1.000	32.1	1.000
Primary health sector total	**48.9**	**75.5**	0.000	**49.6**	0.963	**56.1**	0.000	**562.7**	**669.7**	0.000	**593.8**	0.614	**581.8**	0.000
Thereof primary														
Physiotherapy	5.2	33.7	0.000	7.7	0.000	14.2	0.000	66.2	175.4	0.000	68.5	1.000	60.8	0.000
Chiropractic	0.5	0.5	1.000	0.5	0.768	0.5	0.946	6.2	6.9	0.999	6.0	1.000	5.7	0.942
General practitioner	18.5	16.7	0.000	17.5	0.000	17.3	0.000	215.8	206.4	0.783	222.9	0.977	221.1	0.000
Other primary	24.7	24.5	1.000	23.9	0.560	24.0	0.816	274.6	281.0	1.000	296.3	0.809	294.2	0.818
Prescription medications total	**28.8**	**29.5**	0.998	**29.9**	0.873	**29.8**	0.943	**314.5**	**346.9**	0.782	**367.7**	0.161	**372.8**	0.938
Thereof prescription														
Painkiller medications	3.4	3.6	1.000	3.8	0.985	3.7	0.995	34.8	38.4	0.940	40.2	0.616	39.3	0.996
Not painkiller medications	25.4	25.9	1.000	26.2	0.982	26.1	0.993	279.8	308.5	0.869	327.5	0.252	333.5	0.994
Health costs total (somatic)	**259.2**	**263.0**	1.000	**357.6**	0.000	**333.8**	0.000	**3,260.3**	**4,147.0**	0.001	**4,406.6**	0.000	**4,056.4**	0.000
Home care														
Home care total	**2.5**	**3.2**	0.851	**4.6**	0.001	**4.2**	0.002	**30.7**	**60.1**	0.718	**107.7**	0.016	**203.3**	0.015
Thereof home care														
Home care – Care	1.0	1.6	0.965	2.5	0.008	2.2	0.013	8.3	29.8	0.756	69.4	0.019	151.7	0.147
Home care - Practical help	1.5	1.7	0.974	2.1	0.078	2.0	0.141	22.4	30.3	0.982	38.4	0.390	51.7	0.003
	Hip (n: 4,093)							Hip (n: 658)						
Health costs (somatic)														
Inpatient Admissions total	**79.8**	**127.1**	0.000	**274.4**	0.000	**237.4**	0.000	**1,099.4**	**3,047.2**	0.000	**2,699.7**	0.000	**2,141.7**	0.000
Thereof inpatient														
Surgery knee/hip	13.0	77.2	0.000	181.5	0.000	155.3	0.000	162.5	1,901.2	0.000	1,391.5	0.000	901.2	0.000
Surgery other	6.8	2.7	0.198	10.4	0.732	8.4	0.998	95.8	122.7	1.000	131.9	1.000	137.1	0.999
Outpatient Services total	**96.4**	**87.0**	0.676	**114.8**	0.040	**107.8**	0.453	**1,169.9**	**1,259.9**	1.000	**1,420.9**	0.947	**1,478.7**	0.463
Thereof outpatient														
Surgery knee/hip	0.3	0.7	0.999	0.9	0.750	0.8	0.661	6.8	9.9	1.000	0.0	0.996	0.0	0.673
Surgery other	1.7	3.0	0.855	2.2	0.996	2.4	0.874	28.2	18.3	1.000	17.1	0.999	15.0	1.000
Primary health sector total	**49.1**	**79.9**	0.000	**51.9**	0.000	**58.9**	0.000	**571.3**	**701.2**	0.000	**611.1**	0.934	**594.4**	0.000
Thereof primary														
Physiotherapy	6.4	37.5	0.000	8.8	0.000	16.0	0.000	89.6	208.1	0.000	91.3	1.000	72.0	0.000
Chiropractic	0.7	0.5	0.031	0.5	0.001	0.5	0.001	8.1	7.2	1.000	4.6	0.034	6.4	0.002
General practitioner	18.0	16.9	0.041	17.9	1.000	17.7	0.970	206.9	205.7	1.000	233.1	0.759	218.7	0.972
Other primary	23.9	24.9	0.983	24.7	0.993	24.7	0.986	266.6	280.3	1.000	292.1	0.973	297.3	0.988
Prescription medications total	**28.7**	**29.6**	1.000	**30.3**	1.000	**30.1**	0.977	**316.9**	**358.8**	0.989	**335.2**	1.000	**349.8**	0.980
Thereof prescription														
Painkiller medications	3.1	4.1	0.000	3.9	0.000	4.0	0.000	33.4	44.6	0.530	37.1	1.000	35.8	0.000
Not painkiller medications	25.7	25.6	1.000	26.3	1.000	26.1	1.000	283.5	314.2	1.000	298.1	1.000	314.0	1.000
Health costs total (somatic)	**254.1**	**323.6**	0.000	**471.5**	0.000	**434.2**	0.000	**3,157.5**	**5,367.0**	0.000	**5,066.9**	0.000	**4,564.6**	0.000
Home care														
Home care total	**3.4**	**4.0**	1.000	**4.9**	0.977	**4.7**	0.994	**78.3**	**108.9**	1.000	**189.1**	1.000	**265.0**	0.994
Thereof home care														
Home care – Care	1.8	2.1	1.000	2.7	0.999	2.6	1.000	53.1	79.5	1.000	152.3	0.995	218.6	1.000
Home care - Practical help	1.6	1.9	1.000	2.2	0.710	2.1	0.869	25.2	29.3	1.000	36.8	0.999	46.4	0.994

38 **Table S4. Adjusted health care costs and home care costs one year prior to and one or three years following GLA:D® for knee and hip patients**

	One-year horizon							Three-year horizon						
	Pre-period (1 year)	Post-period (mth 1-3)		Post-period (mth 4-12)		Post-period (year1)		Pre-period (1 year)	Post-period (year 1)		Post-period (year 2)		Post-period (year 3)	
	Cost (€/month)	Cost (€/month)	p-value	Cost (€/month)	p-value	Cost (€/month)	p-value	Cost (€/Year)	Cost (€/year)	p-value	Cost (€/year)	p-value	Cost (€/year)	p-value
	Knee[#]									**Knee[§]**				
Health costs (somatic)														
Inpatient Admissions total	**70.2**	**61.6**	0.097	**159.9**	0.000	**135.2**	0.000	**935.1**	**1,657.4**	0.000	**2,105.4**	0.000	**1,671.9**	0.000
Thereof inpatient														
Surgery knee/hip	9.1	17.5	0.000	68.2	0.000	55.5	0.000	176.2	610.9	0.000	739.9	0.000	456.0	0.000
Surgery other	8.9	3.9	0.002	10.1	0.340	8.5	0.767	112.1	152.2	0.318	153.9	0.294	211.4	0.052
Outpatient Services total	**105.7**	**86.7**	0.000	**103.0**	0.328	**98.9**	0.006	**1,415.7**	**1,307.8**	0.273	**1,337.8**	0.486	**1,352.6**	0.515
Thereof outpatient														
Surgery knee/hip	0.7	0.2	0.000	0.3	0.000	0.3	0.000	80.6	17.8	-	7.4	-	6.7	-
Surgery other	1.7	1.5	0.692	1.4	0.370	1.5	0.376	25.4	18.8	0.453	28.8	0.736	38.0	0.291
Primary health sector total	**59.4**	**92.4**	0.000	**60.3**	0.041	**68.3**	0.000	**608.8**	**720.2**	0.000	**632.4**	0.031	**621.8**	0.275
Thereof primary														
Physiotherapy	6.5	42.5	0.000	9.5	0.000	17.7	0.000	70.0	190.5	0.000	71.8	0.584	64.3	0.103
Chiropractic	0.5	0.5	0.144	0.5	0.004	0.5	0.003	5.7	6.3	0.221	5.6	0.870	5.1	0.264
General practitioner	18.3	16.5	0.000	17.3	0.000	17.1	0.000	235.4	223.5	0.002	240.2	0.256	238.6	0.468
Other primary	33.7	33.8	0.874	32.8	0.029	33.1	0.082	297.9	298.9	0.904	314.6	0.066	313.6	0.118
Prescription medications total	**29.5**	**30.4**	0.008	**30.6**	0.000	**30.6**	0.000	**363.0**	**396.8**	0.000	**415.2**	0.000	**419.3**	0.000
Thereof prescription														
Painkiller medications	3.5	3.8	0.000	3.9	0.000	3.9	0.000	43.2	47.9	0.001	49.8	0.001	49.2	0.004
Not painkiller medications	25.8	26.3	0.061	26.5	0.003	26.4	0.003	318.8	348.1	0.000	364.3	0.000	368.6	0.000
Health costs total (somatic)	**263.3**	**263.7**	0.952	**354.0**	0.000	**331.3**	0.000	**3,391.7**	**4,146.2**	0.000	**4,518.3**	0.000	**4,127.5**	0.000
Home care														
Home care total	**2.7**	**3.6**	0.029	**5.0**	0.001	**4.6**	0.001	**35.5**	**77.2**	**0.011**	**131.1**	0.000	**214.6**	0.000
Thereof home care														
Home care – Care	0.9	1.4	0.004	2.1	0.082	2.0	0.153	8.5	41.1	0.014	90.2	0.000	149.0	0.000
Home care - Practical help	1.8	2.2	0.029	2.8	0.000	2.6	0.000	28.1	44.5	0.052	53.0	0.001	68.1	0.000
	Hip[#]									**Hip[§]**				
Health costs (somatic)														
Inpatient Admissions total	**71.7**	**111.3**	0.000	**243.2**	0.000	**208.9**	0.000	**978.4**	**2,818.4**	0.000	**2,461.1**	0.000	**1,966.0**	0.006
Thereof inpatient														
Surgery knee/hip	11.6	67.0	0.000	167.5	0.000	142.3	0.000	138.1	1,734.6	0.000	1,294.2	0.000	788.5	0.000
Surgery other	6.9	1.3	0.001	11.8	0.086	9.2	0.353	89.2	145.3	0.342	129.6	0.465	139.2	0.370
Outpatient Services total	**77.1**	**68.9**	0.006	**91.2**	0.000	**85.4**	0.012	**1,174.6**	**1,270.1**	0.401	**1,441.3**	0.074	**1,513.5**	0.038
Thereof outpatient														
Surgery knee/hip[&]	0.0	0.0	0.238	0.2	0.000	0.1	0.000	-	-		-		-	
Surgery other	0.4	0.3	0.799	0.4	0.927	0.4	0.881	37.7	29.6	0.643	24.5	0.383	22.1	0.395
Primary health sector total	**58.7**	**96.3**	0.000	**62.4**	0.000	**70.9**	0.000	**584.9**	**719.9**	0.000	**625.2**	0.021	**608.4**	0.231
Thereof primary														
Physiotherapy	8.1	47.7	0.000	11.0	0.000	20.2	0.000	94.5	221.7	0.000	96.4	0.805	74.8	0.003
Chiropractic	0.5	0.4	0.000	0.4	0.000	0.4	0.000	8.9	7.3	0.143	4.9	0.000	6.6	0.144
General practitioner	17.3	16.3	0.000	17.2	0.346	16.9	0.019	214.1	212.0	0.728	228.4	0.020	224.9	0.120
Other primary	32.4	33.9	0.120	34.0	0.038	33.9	0.029	269.0	283.3	0.386	294.0	0.098	300.4	0.056
Prescription medications total	**28.3**	**28.9**	0.333	**29.6**	0.005	**29.4**	0.023	**337.5**	**381.9**	0.016	**350.5**	0.642	**368.7**	0.298
Thereof prescription														
Painkiller medications	2.9	3.8	0.000	3.7	0.000	3.7	0.000	38.0	49.2	0.000	41.8	0.189	41.5	0.327
Not painkiller medications	25.2	24.8	0.452	25.7	0.330	25.4	0.747	298.0	332.1	0.058	306.2	0.766	324.5	0.365
Health costs total (somatic)	**234.5**	**297.6**	0.000	**433.0**	0.000	**397.3**	0.000	**3,051.0**	**5,207.7**	0.000	**4,902.1**	0.000	**4,473.4**	0.001
Home care														
Home care total	**1.1**	**1.7**	0.255	**1.9**	0.009	**1.9**	0.009	**82.4**	**111.4**	0.012	**214.5**	0.000	**406.0**	0.041
Thereof home care														
Home care – Care	0.3	0.3	0.881	0.4	0.195	0.4	0.264	55.1	79.1	0.099	173.3	0.062	356.3	0.064

Home care - Practical help	1.1	1.4	0.067	1.7	0.010	1.7	0.008	28.7	33.1	0.001	46.1	0.000	61.0	0.012

[#]Adjusted health care costs and costs for home care in one-year horizon for women, 65 years, married/co-living, Danish ethnicity, low education and living in the Capital Region estimated using a generalized estimating equation gamma regression model for repeated measures including sex, age, marital status, ethnicity, education and region as covariates. Because of no convergence in the model material status and ethnicity were omitted estimating costs for home care.

[§]Adjusted health care costs and costs for home care in three-year horizon for women, 65 years, married/co-living and low education estimated using a generalized estimating equation gamma regression model for repeated measures including sex, age and education. Because of no convergence in the model age and education were omitted estimating costs for home care.

[&]Surgery is not predicted in a three-year horizon because of no convergence of the model.

Table S5. Sensitivity analysis - adjusted estimated health care cost per QALY from baseline to 12 months for knee and hip patients attending GLA:D® in private clinics, municipal clinics and patients with complete information

	Knee			Hip		
	Change in health care costs (€) (95 % CI)	Change in EQ-5D (QALY) (95 % CI)	Euro pr. QALY (95 % CI)	Change in health care costs (€) (95 % CI)	Change in EQ-5D (QALY) (95 % CI)	Euro pr. QALY (95 % CI)
Private clinic[§]	267	0.036	7,464	651	0.028	22,914
	(181-385)	(0.033-0.038)	(5,485-10,132)	(398-1,050)	(0.024-0.033)	(16,583-31,818)
Municipal clinic[#]	396	0.032	12,292	443	0.028	15,550
	(118-949)	(0.026-0.039)	(4,538-24,333)	(69-2,056)	(0.017-0.043)	(4,059-47,814)
Complete cases[¤]	167	0.035	4,829	579	0.027	21,067
	(74-310)	(0.032-0.037)	(2,313-8,378)	(284-1,142)	(0.023-0.032)	(12,348-35,388)

All analyses are adjusted for age, gender, marital status, ethnicity, educational level and region

[§]Analysis restricted to patients attending GLA:D® in a private clinic

[#]Analysis restricted to patients attending GLA:D® in a private clinic

[¤]Analysis restricted to patients with complete information on EQ-5D

CHEERS Checklist

CHEERS checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Title, page 1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Abstract, page 2
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Line 75-81
		Present the study question and its relevance for health policy or practice decisions.	Line 88-91
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Line 125 –142
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Line 110-117
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Line 97-102
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Line 97-102

Section/item	Item No	Recommendation	Reported on page No/ line No
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Line 97-102
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	N/A
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Line 97-102;
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Line 183-188
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	-
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	N/A
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Line 146-181
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for	-

Section/item	Item No	Recommendation	Reported on page No/ line No
		valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Line 154-158
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	N/A
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	N/A
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Line 210-219; Line 229-235
Results			
Study parameters	18	Report the values, ranges, references, and if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Line 146-181

Section/item	Item No	Recommendation	Reported on page No/ line No
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Table 3; Table 4; Figure 2; Table S2; Table S3
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	N/A
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	-
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Line 237-241
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Discussion
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and	Line 455-456

Section/item	Item No	Recommendation	Reported on page No/ line No
		reporting of the analysis. Describe other non-monetary sources of support.	
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Line 469-483

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist