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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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4 1 **COST-EFFECTIVENESS OF AN 8-WEEK SUPERVISED EDUCATION AND**
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7 2 **EXERCISE THERAPY PROGRAM FOR KNEE AND HIP**
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10 3 **OSTEOARTHRITIS: A PRE-POST ANALYSIS OF 16,255 PATIENTS**
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12 4 **PARTICIPATING IN GOOD LIFE WITH OSTEOARTHRITIS IN**
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15 5 **DENMARK (GLA:D®)**

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52 19 **Original research article for BMJ Open**

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22 ABSTRACT

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

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

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

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

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

37 **Results:** Adjusted change in health care cost was 298€ (95% CI: 206-419)/640€ (400-1,009) and
38 change in EQ-5D was 0.035 (0.033-0.037)/0.028 (0.025-0.032) for knee and hip patients
39 respectively. Hence estimated adjusted health care costs per QALY gained was 8,497€ (6,242-
40 11,324) for knee and 22,568€ (16,000-31,531) for hip patients. Restricting the regression analysis to
41 patients with high compliance, the adjusted health care costs per QALY gained decreased to 5,438€
42 (2,758-9,231) for knee and 17,330€ (10,041-29,364) for hip patients primarily due to lower change

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4 43 in costs. Health care costs per QALY were below conventional thresholds for willingness-to-pay at
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6 44 22,804€ (20,000£) and 43,979€ (50,000 USD).
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10 45 **Conclusions:** A structured 8-week supervised education and exercise therapy program delivered in
11
12 46 primary care was cost-effective at one year in patients with knee or hip OA supporting large scale
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14 47 implementation in clinical practice.
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20 49 **Keywords:** knee, hip, osteoarthritis, exercise therapy, patient education, cost-effectiveness
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26 27 51 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

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30 52 • The study included a large number of rural and urban patients with knee or hip OA treated
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32 in primary care across Denmark.
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35 54 • All costs reported are real-life costs retrieved on an individual level from a range of high-
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37 quality national registries.
- 38 55
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40 56 • The study is a pre-post study reporting change in health care costs against change in generic
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42 health related quality of life (EQ-5D).
- 43 57
44 58 • Health care costs per Quality-Adjusted Life Year (QALY) was reported in a one-year
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46 horizon and additional change in health care costs were reported in a three-year horizon.
- 47 59
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49 60 • 23% and 39 % of the patients did not provide data on EQ-5D immediately following the
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51 intervention and at one year respectively, and the missing data was imputed with Multiple
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53 Imputations.
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63 INTRODUCTION

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65 Knee and hip osteoarthritis (OA) are major contributors to disability and chronic pain worldwide
66 and the implications for both the patients and health care systems are severe,[1,2]. The cost related
67 to OA is estimated to be between 1% and 2.5% of a country's gross domestic product (GDP) in
68 high-income countries,[1], and total annual costs in Europe are estimated to be up to 817 billion €
69 (2013),[3]. The number of people living with OA has increased over the last years and is expected
70 to increase substantially in the future due to an ageing and more overweight and obese
71 population,[4]. This will have extensive societal impact, emphasizing the need for identifying and
72 implementing cost-effective treatment options that can help relieve the pressure health care services
73 around the world are facing,[4].

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75 Clinical guidelines recommend a stepwise treatment approach, including education and exercise
76 therapy as first-line treatment for knee and hip OA,[5-8] with substantial evidence supporting the
77 effects of supervised exercise therapy on pain and physical function,[9-10]. However, studies of
78 quality of care report that exercise therapy is underutilized, estimated to be provided to less than
79 40% of patients with OA,[11,12]. To support the implementation of clinical guidelines into clinical
80 practice, Good Life with osteoArthritis in Denmark (GLA:D[®]) was initiated in 2013 and has been
81 implemented across Denmark. The treatment part of GLA:D[®] is an 8-week supervised patient
82 education and exercise therapy program delivered in primary care for patients with knee or hip OA
83 and has shown positive results on pain, physical function, quality of life (QOL), intake of
84 painkillers and sick leave,[13].

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4 86 Results from previous evaluations of the cost-effectiveness of first-line treatment including exercise
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6 87 therapy and targeting knee or hip OA are heterogeneous, and little is known about the cost-
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9 88 effectiveness of supervised education and exercise therapy implemented in primary care,[14,15].
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11 89 Such evaluation is warranted when deciding whether to implement a structured first-line treatment
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13 90 program, and therefore the aim of the study was to evaluate the cost-effectiveness of GLA:D[®]. We
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16 91 hypothesized that GLA:D[®] would be cost-effective for both knee and hip OA patients.
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21 93 **METHOD**

25 94 26 27 28 95 **Study Design**

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34 97 This is a register-based pre-post study evaluating the cost-effectiveness of an 8-week supervised
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36 98 education and exercise therapy program (GLA:D[®]) for patients with symptomatic knee or hip OA
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39 99 by linking patient level data from the GLA:D[®] registry to national registries in Denmark. We
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41 100 reported mean actual health care costs and costs to home care and public transfer payments in a
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43 101 three-year horizon and reported health care costs per QALY gained in a one-year horizon calculated
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46 102 as the ratio of change in health care costs to change in QOL. The study conforms to the CHEERS
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48 103 statement for reporting health economic evaluations and recommendations for reporting cost-
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50 104 effectiveness analyses,[16,17].
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56 106 **Intervention**

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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 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.

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Population

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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

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4 130 symptoms that are more pronounced than the OA symptoms (e.g. chronic generalized pain or
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6 131 fibromyalgia), or 3) do not understand Danish. According to international,[20] and Danish,[21]
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9 132 guidelines radiographs are not needed for a clinical diagnosis of OA, and therefore not part of the
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11 133 GLA:D® eligibility criteria. The current study included patients enrolled between February 4, 2014,
12
13 134 when collection of the EuroQoL 5-Dimensions 5-Level questionnaire (EQ-5D) was initiated, and
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16 135 December 31, 2016, allowing for one year follow up since information on all costs was available
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18 136 until the end of 2017. Patients with available baseline information on EQ-5D and information on
19
20 137 whether a knee or a hip joint was the most affected joint were included in the study. Reporting
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23 138 mean costs in a three-year horizon was restricted to patients entering the program before December
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25 139 31, 2014, allowing for three-year follow up, and reporting costs for public transfer payments were
26
27 140 restricted to patients aged 18 to 63 years both in the pre- and post-intervention period to ensure that
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30 141 they did not turn 65 during the post-period which was the retirement age in Denmark in 2017. To
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32 142 cover living expenses public transfer payments are in Denmark provided to adults under the age of
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34 143 retirement who e.g. are unemployed, have low/no ability to work or are enrolled in education.
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40 145 **Variables**

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45 147 Data in the GLA:D® registry are collected at baseline, following the intervention (~3 months), and
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48 148 at 12 months and includes demographics, a mix of therapist and patient-reported health measures
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50 149 and outcome measures as well as compliance,[13]. Via the Civil Registration number (CPR), which
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52 150 identifies every citizen in Denmark, the GLA:D® registry was linked to national registries from
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55 151 where actual individual level utilization of somatic health care services (including use of primary
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57 152 health care services, secondary health care services, and use of preceptive medication; i.e. excluding
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4 153 use of psychiatric health care services), home care, and public transfer payments were
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7 154 retrieved,[22]. In Denmark home care including practical help and personal care is offered to
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9 155 citizens with low functional level who are unable to manage everyday life on their own. All prices
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11 156 and costs were converted into Euros (€) and reported in present values (2017-level) based on the
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13 157 Danish Consumer Price Index. Costs were given as mean costs per month (one-year horizon) or
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16 158 year (three-year horizon) and public transfer payments were given as full-time weeks (37 h per
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18 159 week) per month (one-year horizon) or per year (three-year horizon).
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20 160 Costs related to primary health care services, including visits to physiotherapist, chiropractor,
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23 161 general practitioner, and others (e.g. medical specialist, laboratory work, dentist), were obtained
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25 162 from the Danish National Health Insurance Service Registry. Within the primary health care sector
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27 163 in Denmark physiotherapy is delivered both in private clinics and in municipality settings however,
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30 164 costs for interventions delivered in municipal settings were not available and therefore not included
31
32 165 in the analysis. Services and admissions related to secondary health care, including total somatic
33
34 166 inpatient and outpatient services, were obtained from the Danish National Patient Registry and
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36 167 associated costs were estimated based on the Danish Case Mix System. The Danish National Patient
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38
39 168 Registry holds information on all inpatient admissions and outpatient activities, including accident
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41 169 and emergency visits in Danish hospitals. Every contact is coded in a classification system
42
43 170 incorporating ICD-10 codes and use of resources in contacts where surgery in the knee or hip
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46 171 occurred were reported separately. Costs for prescriptive medications were obtained from the
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48 172 Danish National Prescription Registry holding information on all prescriptions on medications,
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50 173 including date of purchase, number of packages and the reimbursement paid by public funds. All
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53 174 drugs are classified according to the Anatomical Therapeutic Chemical Classification System
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55 175 (ATC) and painkillers (ATC-codes: N02A, N02B, M01A, M02AA) and other medications were
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57 176 reported separately. Information on number and duration of visits for personal care and practical
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4 177 help, respectively, was retrieved from Statistics Denmark and the average care costs per hour (2017)
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6 178 in Denmark was used to calculate costs. Information on nursing care was not available and therefore
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9 179 not included in the analysis. Information on public transfer payments was retrieved from the
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11 180 Registry for Public Transfers, which holds information on type and hours of public transfer
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13 181 payments and was reported as the number of weeks receiving transfer payment (unemployment,
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16 182 sheltered employment, sick leave, rehabilitation, education, disability pension, early retirement).
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20 184 Outcome was reported as QALYs gained measured with EQ-5D converted into an index score using
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23 185 time-trade-off based weights from the Danish crosswalk value set (-0.624 to 1; worst to best),[23].
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25 186 The EQ-5D comprises of five dimensions: Mobility, self-care, usual activities, pain discomfort and
26
27 187 anxiety/depression each having five levels of response options from ‘no problems’ to ‘severe
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30 188 problems’,[24]. QALYs combine time lived and QOL into a single index number where ‘1’
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32 189 corresponds to one year of full health and ‘0’ corresponds to being dead.
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36 191 Information on the covariates age (continuous), sex (male or female), marital status
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41 193 (primary, secondary, vocational, short-term, bachelor, long-term or unknown) and administrative
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43 194 region (Capital, Zealand, Southern Denmark, Central Denmark or North Denmark) were retrieved
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46 195 from the Danish Civil Registration System. Most affected joint (knee or hip) and information on
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48 196 compliance were therapist-reported and high compliance was defined as patients attending at least
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50 197 10 supervised exercise sessions. Type of clinic (private or municipal) was retrieved from the
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53 198 GLA:D® registry and whether the patient died during follow up was retrieved from the Danish Civil
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55 199 Registration System.
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4 201 **Statistical analyses**

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10 203 Descriptive statistics for baseline characteristics, average and predicted costs from somatic health
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12 204 care services and home care and average and predicted weeks receiving public transfer payments
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15 205 one year prior to and one or three years after entering the program, respectively, were reported. To
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17 206 take the potential influence of covariates into account, costs and weeks receiving public transfer
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20 207 payments were predicted using a generalized estimating equation (GEE) gamma regression model
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22 208 for repeated measures. Statistically significant difference between costs in the pre- and post-
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24 209 intervention period was assessed using bootstrap t-test.

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31 211 We estimated health care costs per QALY gained as the ratio of change in total health care costs to
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33 212 change in QOL. Change in health care costs was calculated as the mean cost difference between the
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35 213 year prior to and the year after entering the intervention. QALYs gained was calculated as the mean
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38 214 difference between the EQ-5D score at baseline, before initiating the program, representing the
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40 215 QOL the year prior to the intervention and the EQ-5D score at 3 and 12 months calculated as ‘the
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42 216 area under the curve’ taking change over time into account, representing the QOL the year after
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45 217 entering the program. Data were not normal distributed and changes in costs and EQ-5D were
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47 218 estimated using a GEE gamma regression model for repeated measures. Raw and adjusted analyses
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49 219 including gender, age, marital status, ethnicity, educational level and region as covariates were
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52 220 conducted. In case of no convergence in the model, selected covariates were omitted.

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4 222 There is no official threshold for willingness-to-pay in Denmark and we compared the health care
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6 223 cost per QALY to predefined willingness-to-pay thresholds of a cost-effective treatment defined by
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9 224 the National Institute for Health and Care Excellence (NICE) at 22,804€ (20,000£) per QALY,[25]
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11 225 and the widely used threshold of 43,979€ (50,000 USD) per QALY,[26]. To explore if adherence to
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13 226 the exercise therapy component had an impact on the results, a sub-analysis repeating all analyses
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16 227 restricted to patients with high compliance was conducted. All analyses were reported separately for
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18 228 knee and hip patients.
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25 230 As previously proposed for cost-effectiveness studies and clinical trials in OA,[27,28] missing
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27 231 values for the EQ-5D index score at follow up were imputed using Multiple Imputations (MI) with
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29 232 chained equations under the assumption of data being missing at random,[29]. Since EQ-5D was
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31 233 not normal distributed, Predictive Mean Matching was applied, and all baseline variables presented
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34 234 in the study and outcome variables of interest were included in the model. In total, 40 datasets were
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36 235 generated, approximately equal to the largest percentages of missing observations for the outcome
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38 236 as recommended,[30].
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43 238 Since costs for health care services delivered in municipal settings were not available, all analyses
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45 239 were repeated stratified for patients attending GLA:D® in private physiotherapy clinics vs. in
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48 240 municipal rehabilitation centers. To explore the impact of missing data, a sensitivity analysis
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50 241 repeating all analyses restricted to complete cases was conducted and all analyses were repeated
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52 242 excluding patients who died during follow up.
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244 The significance level for all statistical analyses was defined a priori at $p < 0.05$. All analyses were
245 performed using the SAS 9.4 (SAS Institute, North Carolina, USA).

247 RESULTS

249 12,162 knee patients and 4,093 hip patients were included in the study and follow up data on EQ-
250 5D were available for 77% immediately after treatment and 61% at one year (Figure 1). Patients
251 with complete information had slightly better, but most likely not clinically relevant better health
252 status at baseline compared to patients with incomplete information (Table S1, Supplementary
253 Appendix). Baseline characteristics are presented in Table 1. Three quarters of the patients were
254 female, median symptom duration was 2 years, almost two thirds reported use of pain medication
255 and 31% and 4% of knee and hip patients, respectively, reported previous surgery in most affected
256 joint.

258 [Figure 1]

259 [Table 1]

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

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4 265 the potential influence of covariates into account, costs are predicted for average patients, i.e.
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7 266 women, 65 years old, married/co-living, ethnic Danish, low educational level and living in the
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9 267 Capital Region. Public transfer payments are predicted for women, 55 years old, married/co-living,
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11 268 ethnic Danish, low educational level and living in the Capital Region since the population was
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13 269 restricted to adults under the age of retirement in this analysis, as public transfer payments target
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15
16 270 this age group. In the one-year horizon, monthly predicted health care costs for knee and hip
17
18 271 patients were 263€/235€ one year prior to the intervention, rising to 331€/397€ the year after
19
20 272 entering the program (Table S3, Supplementary Appendix). In the three year horizon, yearly
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22
23 273 predicted health care costs one year prior to the intervention were 3,392€/3,051€ for knee and hip
24
25 274 patients, rising to 4,128€/4,473€ the third year after entering the intervention, observing the highest
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27 275 costs the second year post-intervention for knee patients and the first year post-intervention for hip
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29
30 276 patients (Figure 2a and 2b). The increase in mean health care costs was mainly due to costs related
31
32 277 to surgeries in the knee or hip. On average, the raw EQ-5D score increased from 0.711 to 0.756
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34 278 points for knee patients and from 0.705 to 0.747 for hip patients from baseline to one year follow up
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37 279 (Table 3).

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42 281 [Figure 2]

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45 282 [Table 2]

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48 283 [Table 3]

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54 285 Adjusted change in health care cost from the year prior to entering GLA:D[®] to the year after
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56 286 entering GLA:D[®] was 298€ (95% CI: 206-419)/640€ (400-1,009) and QALYs gained were 0.035
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59 287 (0.033-0.037)/0.028 (0.025-0.032) for knee and hip patients, respectively. Hence, one-year
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4 288 estimated adjusted health care costs was 8,497€ (6,242-11,324) for knee patients and 22,568€
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6 289 (16,000-31,531) for hip patients per QALY gained (Table 4). Restricting the regression analysis to
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9 290 patients with high compliance, the one-year adjusted health care costs per QALY gained was lower;
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11 291 5,438€ (2,758-9,231) for knee patients and 17,330€ (10,041-29,364) for hip patients primarily due
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13 292 to lower change in health care costs (Table 4). Although the upper limit of the 95% CI for hip
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16 293 patients was in between the two predefined willingness-to-pay thresholds, the estimated health care
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18 294 costs per QALY for both knee and hip patients were below both of the two predefined willingness-
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20 295 to-pay thresholds.

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26 297 [Table 4]

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32 299 Sensitivity analyses showed that knee and hip patients attending GLA:D® in a private clinic had
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34 300 similar health care costs per QALY but that patients attending GLA:D® in a municipal setting had
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37 301 higher costs for knee patients and lower costs for hip patients compared to all patients. This
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39 302 difference was primarily explained by different change in health care costs (Table S5,
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41 303 Supplementary Appendix). The complete case analysis showed lower change in health care costs
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43 304 and lower health care costs per QALY for knee patients (4,829€ (2,313-8,378)) but for hip patients
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46 305 the ratio was similar to that of all patients (Table S5, Supplementary Appendix). 53 patients died
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48 306 within the one-year follow up period and 11 of these within the first 3 months. Repeating all
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51 307 analyses excluding deaths in the regression analyses showed results similar to the main analysis
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53 308 (data not shown).

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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,

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

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

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4 354 As a result of similar change in EQ-5D, but lower change in health care costs, health care costs per
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6 355 QALY were lower in patients compliant to the intervention compared to all patients enrolled in the
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9 356 program, indicating that the dosage of exercise therapy is important. Although we did not find that
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11 357 higher compliance was associated with greater effects on the EQ-5D, the lower change in health
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13 358 care costs in the compliant patients underlines the importance of exercise dosage as suggested by a
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16 359 systematic review and meta-regression analysis of 48 randomized controlled trials in patients with
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18 360 knee OA showing that 12 or more supervised exercise sessions are more effective than fewer
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20 361 supervised sessions,[43], and a systematic review and meta-analysis in patients with hip OA
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23 362 showing that supervised exercise therapy with high compliance with dose recommendations
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25 363 compared to uncertain compliance was more effective,[44]. Although dosage seems important for
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27 364 the effect and cost-effectiveness, knowledge of optimal exercise dosage in OA is still
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30 365 lacking,[9,43,45].
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35 367 As there is no official threshold defining a cost-effective treatment in Denmark, we compared the
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38 368 health care costs per QALY to two different internationally widely used willingness-to-pay
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40 369 thresholds. Although the estimated health care costs per QALY for both knee and hip patients were
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42 370 below both of the two thresholds, the upper limit of the 95% CI for hip patients was in between the
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45 371 two thresholds, thus we cannot rule out that the true health care costs per QALY for hip patients is
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47 372 above the lower willingness-to-pay threshold (22,804€). A threshold value for willingness-to-pay
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49 373 for improvements in health is arbitrary and depending on the context such as budget and other
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51 374 treatment options,[26]. Country-level threshold value based on GDP per capita has been discussed
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54 375 but remains unsettled,[46]. When deciding which treatment options to implement and offer, the
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56 376 results from this study can support clinicians and decision-makers in terms of one-year cost-
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4 377 effectiveness of supervised education and exercise therapy implemented nationwide for patients
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6 378 with knee and hip OA in clinical practice.
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11 12 380 **Strengths and limitations**

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18 382 The major strength of the study is that all costs reported are real-life costs retrieved on an individual
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20 383 level from a range of high-quality national registries supporting the reliability and validity of the
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22 384 costs,[22,47,48]. Even though it is likely that a higher level of heterogeneity in treatment protocols
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24 385 occurred compared to in rigorous clinical trials, another major strength is that the study included a
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26 386 large number of rural and urban patients with wide inclusion criteria; joint pain and functional
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28 387 limitations associated with OA, retrieved from a nationwide registry supporting the generalizability
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30 388 of the findings.
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38 390 The main limitation of the study is that the study is a pre-post study where change in health care
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40 391 costs was evaluated against change in EQ-5D. Without a proper control group, it cannot be ruled
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42 392 out that the observed change in EQ-5D is related to other factors than the treatment such as
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44 393 regression to the mean. Also, change in costs can potentially have been affected by increasing age,
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46 394 since health care costs are expected to increase with increased age and accompanied morbidity,[49].
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53 396 In the current study, health care costs per QALY was evaluated in a one-year horizon and
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55 397 additionally change in costs were reported in a three-year horizon. OA is a long-term chronic
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57 398 condition,[36], thus evaluating cost-effectiveness in a one-year horizon is a relatively short time
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4 399 horizon warranting further long-term cost-effective analyses. However, a recent model-based cost-
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6 400 effectiveness analysis suggested that a physical activity program for patients with knee OA would
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9 401 lead to favorable long-term clinical and economic benefits,[50].
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15 403 There was a loss to follow up in the GLA:D[®] registry and conducting a sensitivity analysis
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17 404 restricted to patients with complete information revealed that they had less mean change in health
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19 405 care costs than all included patients, indicating a risk of selective loss to follow up in the GLA:D[®]
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22 406 registry, however, the evaluation on health care costs per QALY included all patients enrolled in
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24 407 GLA:D[®], imputing the missing outcome values at follow up. Imputing missing outcome values
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26 408 relied on the assumption that data were missing at random, i.e. the missingness was related to
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29 409 variables included in the model. However, there is a risk that loss to follow up was related to
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31 410 unobserved factors not available for the analysis. One third did not provide information on
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33 411 compliance and there is a risk that lower change in health care costs in the sub-group of patients
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35 412 with high compliance is affected by selection bias. However, we did not find clinically relevant
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38 413 health status differences at baseline among those not providing information on compliance
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40 414 compared to those with this information (data not shown).
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46 416 The current study is based on real-world outcome data collected in nationwide physiotherapy clinics
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48 417 and actual health care costs retrieved from national registries, supporting the generalizability of the
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51 418 results. However, patients attending GLA:D[®] are a preselected group of patients who are commonly
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53 419 referred to physiotherapy for their symptoms with most being able to pay partly for the intervention,
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55 420 which might limit the generalizability.
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4 422 **CONCLUSIONS**

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10 424 A structured 8-week supervised education and exercise therapy program delivered in physiotherapy
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12 425 practice was cost-effective at one year in patients with knee and hip OA compared to conventional
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15 426 willingness-to-pay thresholds. Both health-related QOL and health care costs increased during the
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17 427 one-year time horizon, the latter mainly due to knee or hip surgeries. The results support large scale
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19 428 implementation of a structured supervised evidence-based patient education and exercise therapy
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22 429 program targeting patients with knee or hip OA and can guide clinicians and decision makers on
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24 430 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

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4 451 Drafting the article: DTG, STS
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7 452 Revising the article critically for important intellectual content: DTG, ER, RI, JK, STS
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10 453 Final approval of the article: DTG, ER, RI, JK, STS
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13 454 Obtaining of funding: STS
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24 457
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26
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28
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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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5 650 **TABLE LEGENDS**
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8 651 Table 1. Baseline characteristics in knee and hip patients attending GLA:D®
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11 652 Table 2. Predicted public transfer payments one year prior to and one or three years following
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13 653 GLA:D® for knee and hip patients
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16 654 Table 3. Change in health-related quality of life from baseline to 12 months for knee and hip
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18 655 patients attending GLA:D®
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21 656 Table 4. Adjusted and raw estimated health care costs per QALY from baseline to 12 months for all
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23 657 knee and hip patients attending GLA:D® and for knee and hip patients with high compliance
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659 **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)

660 Missing values: BMI n: 5 (knee), n: 7 (hip); Number of comorbidities n: 711 (knee), n: 215 (hip); Symptom duration
661 (mainly missing due to technical problems): n: 3,157 (knee), n: 1,096 (hip) ; Pain intensity: n:23 (knee), n:9 (hip) ;
662 Bilateral symptoms: n:32 (knee), n:20 (hip) ; Walk speed: n:610 (knee), n:221 (hip); KOOS/HOOS QOL: n: 36 (knee),

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663 n: 21 (hip).

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

665 □Self-reported use of pain medication during last 3 months

666 %Number of comorbidities calculated from self-report of the following conditions: hypertension, cardiovascular
667 diseases, lung diseases, diabetes, stomach diseases, liver- or kidney diseases, blood diseases, cancer, depression,
668 rheumatoid arthritis, neurological disorders, other medical diseases

669 &Self-reported previous surgery in worst joint

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

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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	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	0.344	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	0.977	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	0.205	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	0.607	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	0.507	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	0.999	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	0.100	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	0.377	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	0.600	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	0.523	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	0.521	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:

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

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688 **Table 3. Change in health-related quality of life from baseline to 12 months for knee and hip**
 689 **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

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

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

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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

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700 **FIGURE LEGENDS**

701 Figure 1. Flow chart

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

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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

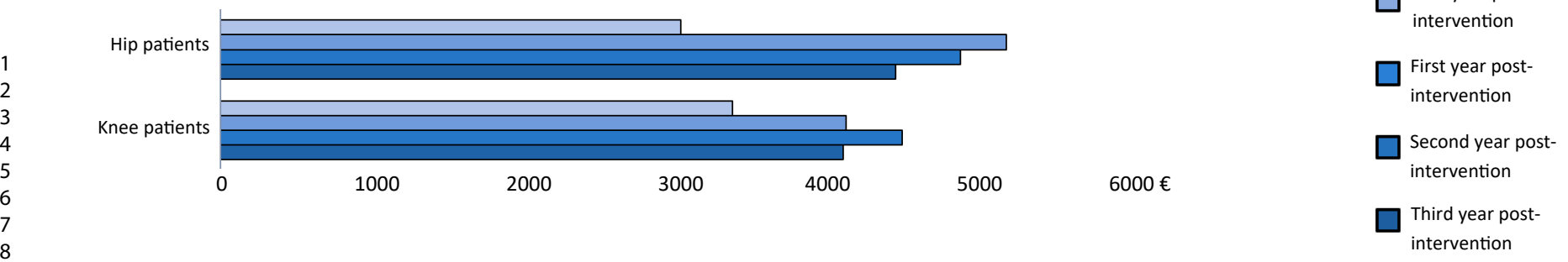
6,990 knee patients had complete information on EQ-5D

2,349 hip patients had complete information on EQ-5D

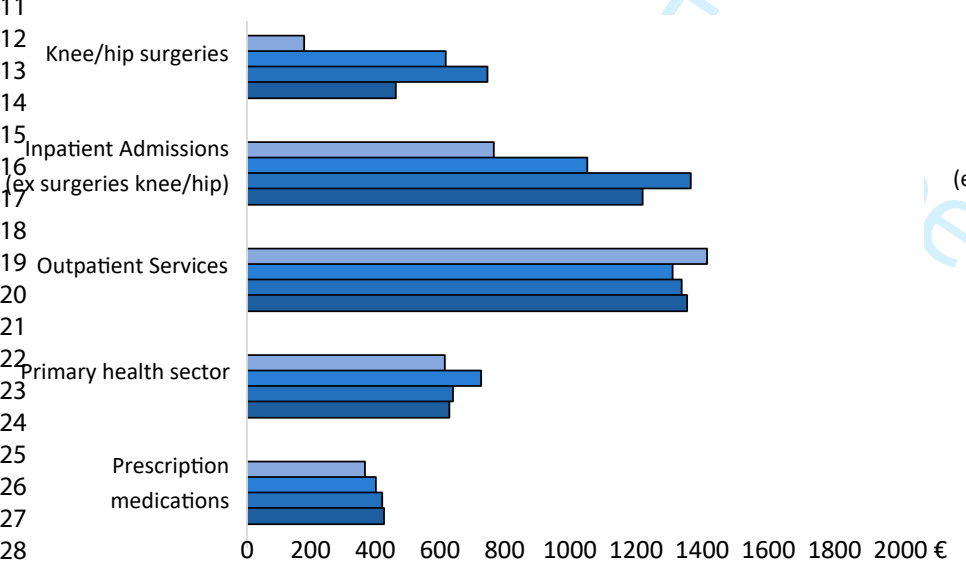


a) Predicted health care costs/year - total

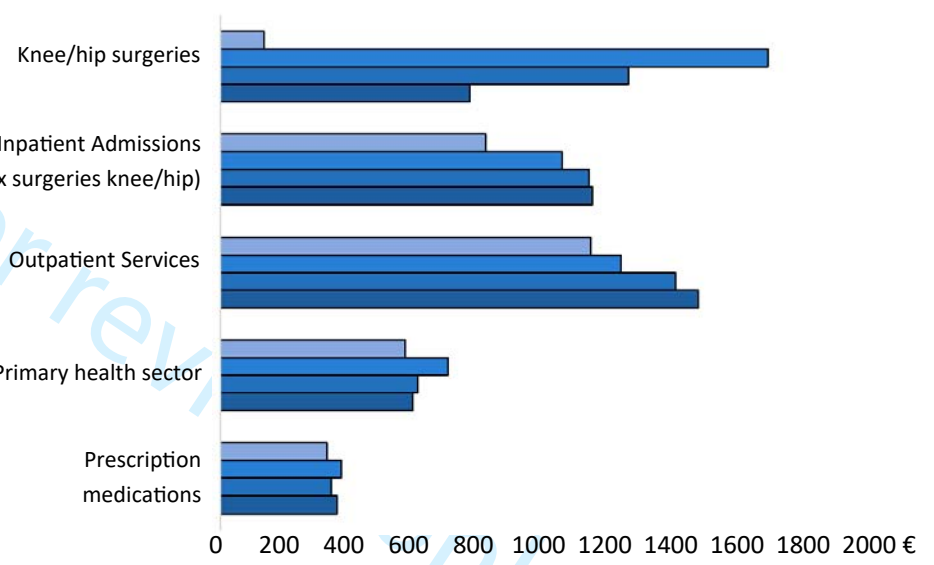
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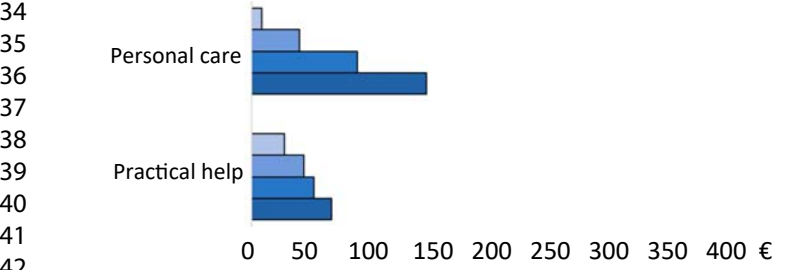
b) Predicted health care costs/year - knee patients



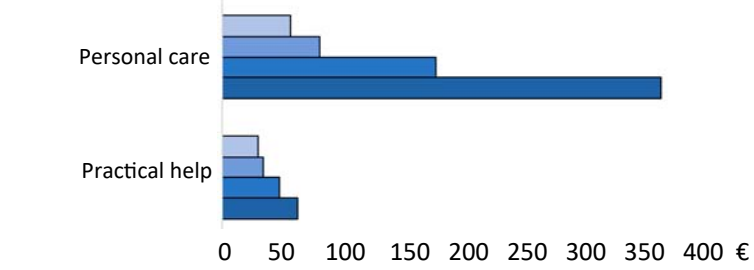
c) Predicted health care costs/year - hip patients



d) Predicted costs/year home care - knee patients



e) Predicted costs/year home care - hip patients



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

15 **Table S1: Baseline characteristics in patients with complete information and patients who had**
 16 **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)

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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^o (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

^oSelf-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	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		

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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
35	#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													
36	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													
37	ethnicity were omitted estimating costs for home care.													
38	§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													
39	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.													
40	¶Surgery is not predicted in a three-year horizon because of no convergence of the model.													

For peer review only

42 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/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	0.000	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	0.000	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	0.000	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	0.000	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	0.000	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	0.000	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	0.000	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	0.000	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		

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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 (181-385)	0.036 (0.033-0.038)	7,464 (5,485-10,132)	651 (398-1,050)	0.028 (0.024-0.033)	22,914 (16,583-31,818)
Municipal clinic[#]	396 (118-949)	0.032 (0.026-0.039)	12,292 (4,538-24,333)	443 (69-2,056)	0.028 (0.017-0.043)	15,550 (4,059-47,814)
Complete cases[‡]	167 (74-310)	0.035 (0.032-0.037)	4,829 (2,313-8,378)	579 (284-1,142)	0.027 (0.023-0.032)	21,067 (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	<i>Single study-based estimates:</i> 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	<i>Synthesis-based estimates:</i> 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	<i>Single study-based economic evaluation:</i> 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	<i>Model-based economic evaluation:</i> 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	<i>Single study-based economic evaluation:</i> 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	<i>Model-based economic evaluation:</i> 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

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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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Primary Subject Heading:	Health economics
Secondary Subject Heading:	Sports and exercise medicine
Keywords:	Knee < ORTHOPAEDIC & TRAUMA SURGERY, Hip < ORTHOPAEDIC & TRAUMA SURGERY, SPORTS MEDICINE, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, HEALTH ECONOMICS

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4 1 **COST-EFFECTIVENESS OF AN 8-WEEK SUPERVISED EDUCATION AND**
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7 2 **EXERCISE THERAPY PROGRAM FOR KNEE AND HIP**
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10 3 **OSTEOARTHRITIS: A PRE-POST ANALYSIS OF 16,255 PATIENTS**
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12 4 **PARTICIPATING IN GOOD LIFE WITH OSTEOARTHRITIS IN**
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15 5 **DENMARK (GLA:D®)**

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55 20 **Original research article for BMJ Open**

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58 21 Word count abstract: 298 words

22 Word count manuscript: 4.256

23 **ABSTRACT**

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

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

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

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

32 **Outcome measures:** Adjusted health care costs per Quality-Adjusted Life Year (QALY) gained
33 from baseline to one year (ratio of change in health care costs to change in EQ-5D). All adjusted
34 measures were estimated using a generalized estimating equation gamma regression model for
35 repeated measures. Missing data on EQ-5D were imputed with Multiple Imputations (3 months:
36 23%; 1 year: 39 %).

37 **Results:** Adjusted change in health care cost was 298€ (95% CI: 206-419) and 640€ (95% CI: 400-
38 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)
39 for knee and hip patients, respectively. Hence estimated adjusted health care costs per QALY
40 gained was 8,497€ (95% CI: 6,242-11,324) for knee and 22,568€ (95% CI: 16,000-31,531) for hip
41 patients. In patients with high compliance, the adjusted health care costs per QALY gained was
42 5,438€ (95% CI: 2,758-9,231) for knee and 17,330€ (95% CI: 10,041-29,364) for hip patients.
43 Health care costs per QALY were below conventional thresholds for willingness-to-pay at 22,804€

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4 44 (20,000£) and 43,979€ (50,000 USD), except the upper limit of the 95% CI for hip patients which
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7 45 was in between the two thresholds.
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10 46 **Conclusions:** A structured 8-week supervised education and exercise program delivered in primary
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12 47 care was cost-effective at one year in patients with knee or hip OA supporting large scale
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14 48 implementation in clinical practice.
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20 50 **Keywords:** knee, hip, osteoarthritis, exercise therapy, patient education, cost-effectiveness
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27 52 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

- 30 53 • The study included a large number of rural and urban patients with knee or hip OA treated
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33 54 in primary care across Denmark.
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35 55 • All costs reported are real-life costs retrieved on an individual level from a range of high-
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37 56 quality national registries.
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40 57 • The study is a pre-post study reporting change in health care costs against change in generic
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42 58 health related quality of life (EQ-5D).
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45 59 • Health care costs per Quality-Adjusted Life Year (QALY) was reported in a one-year
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47 60 horizon and additional change in health care costs were reported in a three-year horizon.
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49 61 • 23% and 39 % of the patients did not provide data on EQ-5D immediately following the
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51 62 intervention and at one year respectively, and the missing data was imputed with Multiple
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54 63 Imputations.
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64 INTRODUCTION

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66 Knee and hip osteoarthritis (OA) are major contributors to disability and chronic pain worldwide
67 and the implications for both the patients and health care systems are severe,[1,2]. The cost related
68 to OA is estimated to be between 1% and 2.5% of a country's gross domestic product (GDP) in
69 high-income countries,[1], and total annual costs in Europe are estimated to be up to 817 billion €
70 (2013),[3]. The number of people living with OA has increased over the last years and is expected
71 to increase substantially in the future due to an ageing and more overweight and obese
72 population,[4]. This will have extensive societal impact, emphasizing the need for identifying and
73 implementing cost-effective treatment options that can help relieve the pressure health care services
74 are facing around the world,[4].

75

76 Clinical guidelines recommend a stepwise treatment approach, including education and exercise
77 therapy as first-line treatment for knee and hip OA,[5-8] with substantial evidence supporting the
78 effects of supervised exercise therapy on pain and physical function,[9-10]. However, studies of
79 quality of care report that exercise therapy is underutilized, estimated to be provided to less than
80 40% of patients with OA,[11,12]. To support the implementation of clinical guidelines into clinical
81 practice, Good Life with osteoArthritis in Denmark (GLA:D®) was initiated in 2013 and has been
82 implemented across Denmark. The treatment part of GLA:D® is an 8-week supervised patient
83 education and exercise therapy program delivered in primary care for patients with knee or hip OA
84 and has shown positive results on pain, physical function, quality of life (QOL), intake of
85 painkillers and sick leave,[13].

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4 87 Results from previous evaluations of the cost-effectiveness of first-line treatment including exercise
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6 88 therapy and targeting knee or hip OA are heterogeneous, and little is known about the cost-
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9 89 effectiveness of supervised education and exercise therapy implemented in primary care,[14,15].
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11 90 Such evaluation is warranted when deciding whether to implement a structured first-line treatment
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13 91 program, and therefore the aim of the study was to evaluate the cost-effectiveness of GLA:D[®]. We
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16 92 hypothesized that GLA:D[®] would be cost-effective for both knee and hip OA patients.
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21 94 **METHOD**

25 95 26 27 28 96 **Study Design**

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34 98 This is a registry-based pre-post study evaluating the cost-effectiveness in a healthcare payer
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36 99 perspective of an 8-week supervised education and exercise therapy program (GLA:D[®]) for patients
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39 100 with symptomatic knee or hip OA by linking patient level data from the GLA:D[®] registry to
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41 101 national registries in Denmark. In the primary analysis, we reported health care costs in a healthcare
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43 102 payer perspective per QALY gained in a one-year horizon calculated as the ratio of change in health
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46 103 care costs to change in QOL in the same patients. In addition, as a secondary analysis, mean actual
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48 104 health care costs and costs to home care and public transfer payments were reported in a three-year
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50 105 horizon to assess how costs develop over time in this population of patients with a chronic
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53 106 condition. The study conforms to the CHEERS statement for reporting health economic evaluations
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55 107 and recommendations for reporting cost-effectiveness analyses,[16,17].
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60**Intervention**

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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.

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Population

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4 131 Patients are eligible for the GLA:D® program if they have a clinical diagnosis of knee and/or hip
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7 132 OA as evaluated by the treating physiotherapist i.e. pain or functional limitations associated with
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9 133 knee or hip OA and do not meet any of the following exclusion criteria: 1) another reason for the
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11 134 joint symptoms than OA (e.g. tumor, inflammatory joint disease or patellar tendinopathy), 2) other
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13 135 symptoms that are more pronounced than the OA symptoms (e.g. chronic generalized pain or
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16 136 fibromyalgia), or 3) do not understand Danish. According to international,[20] and Danish,[21]
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18 137 guidelines radiographs are not needed for a clinical diagnosis of OA, and therefore not part of the
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20 138 GLA:D® eligibility criteria. The current study included patients enrolled between February 4, 2014,
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23 139 when collection of the EuroQoL 5-Dimensions 5-Level questionnaire (EQ-5D) was initiated, and
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25 140 December 31, 2016, allowing for one year follow up since information on all costs was available
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27 141 until the end of 2017. Patients with available baseline information on EQ-5D and information on
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30 142 whether a knee or a hip joint was the most affected joint were included in the study. Reporting
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32 143 mean costs in a three-year horizon was restricted to patients entering the program before December
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34 144 31, 2014, allowing for three-year follow up, and reporting costs for public transfer payments were
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36 145 restricted to patients aged 18 to 63 years both in the pre- and post-intervention period to ensure that
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39 146 they did not turn 65 during the post-period which was the retirement age in Denmark in 2017. To
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41 147 cover living expenses public transfer payments are in Denmark provided to adults under the age of
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43 148 retirement who e.g. are unemployed, have low/no ability to work or are enrolled in education.
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46 149 Please find more information about the Danish health care system elsewhere,[22].
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52 151 **Variables**
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153 Data in the GLA:D[®] registry are collected at baseline, following the intervention (~3 months as the
154 program is implemented in primary care and some variation in follow up time occurs), and at 12
155 months and includes demographics, a mix of therapist and patient-reported health measures and
156 outcome measures as well as compliance,[13]. Via the Civil Registration number (CPR), which
157 identifies every citizen in Denmark, the GLA:D[®] registry was linked to national registries from
158 where actual individual level utilization of somatic health care services (including use of primary
159 health care services, secondary health care services, and use of preceptive medication; i.e. excluding
160 use of psychiatric health care services), home care, and public transfer payments were
161 retrieved,[22]. In Denmark home care including practical help and personal care is offered to
162 citizens with low functional level who are unable to manage everyday life on their own. All prices
163 and costs were converted into Euros (€) and reported in present values (2017-level) based on the
164 Danish Consumer Price Index. Costs were given as mean costs per month (one-year horizon) or
165 year (three-year horizon) and public transfer payments were given as full-time weeks (37 h per
166 week) per month (one-year horizon) or per year (three-year horizon).

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

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4 177 admissions and outpatient activities, including accident and emergency visits in Danish hospitals.
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7 178 Every contact is coded in a classification system incorporating ICD-10 codes and use of resources
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9 179 in contacts where surgery in the knee or hip occurred were reported separately. Costs for
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11 180 prescriptive medications were obtained from the Danish National Prescription Registry holding
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13 181 information on all prescriptions on medications, including date of purchase, number of packages
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16 182 and the reimbursement paid by public funds. All drugs are classified according to the Anatomical
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18 183 Therapeutic Chemical Classification System (ATC) and painkillers (ATC-codes: N02A, N02B,
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20 184 M01A, M02AA) and other medications were reported separately. Individual level information on
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23 185 number and duration of visits for personal care and practical help, respectively, was retrieved from
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25 186 Statistics Denmark and the average care costs per hour (2017) in Denmark was used to calculate
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27 187 costs. Information on nursing care was not available and therefore not included in the analysis.
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30 188 Information on public transfer payments was retrieved from the Registry for Public Transfers,
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32 189 which holds information on type and hours of public transfer payments and was reported as the
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34 190 number of weeks receiving transfer payment (unemployment, sheltered employment, sick leave,
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36 191 rehabilitation, education, disability pension, early retirement).
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41 193 Outcome was reported as QALYs gained measured with EQ-5D converted into an index score using
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43 194 time-trade-off based weights from the Danish crosswalk value set (-0.624 to 1; worst to best),[23].
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46 195 The EQ-5D comprises of five dimensions: Mobility, self-care, usual activities, pain discomfort and
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48 196 anxiety/depression each having five levels of response options from 'no problems' to 'severe
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50 197 problems',[24]. QALYs combine time lived and QOL into a single index number where '1'
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53 198 corresponds to one year of full health and '0' corresponds to being dead.
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200 Information on the covariates age (continuous), sex (male or female), marital status
201 (married/coliving or single), ethnic background (western [countries in EU, associated countries and
202 the four Anglo-Saxon countries] or not western [other countries]), educational level (primary,
203 secondary, vocational, short-term, bachelor, long-term or unknown) and administrative region
204 (Capital, Zealand, Southern Denmark, Central Denmark or North Denmark) were retrieved from the
205 Danish Civil Registration System. Most affected joint (knee or hip) and information on compliance
206 were therapist-reported and high compliance was defined as patients attending at least 10
207 supervised exercise sessions. Type of clinic (private or municipal) was retrieved from the GLA:D®
208 registry and whether the patient died during follow up was retrieved from the Danish Civil
209 Registration System.

211 **Statistical analyses**

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

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4 222 We estimated health care costs per QALY gained as the ratio of change in actual total health care
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6 223 costs to change in QOL. Change in health care costs was calculated as the mean cost difference
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9 224 between the year prior to and the year after entering the intervention. QALYs gained was calculated
10
11 225 as the mean difference between the EQ-5D score at baseline, calculated as ‘the area under the
12
13 226 curve’ taking change over time into account, representing the QOL the year after entering the
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15
16 227 program (Figure S1, Supplementary Appendix). Data were not normal distributed and changes in
17
18 228 costs and EQ-5D were estimated using a GEE gamma regression model for repeated measures.
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21 229 In the first step change in health care costs and change in QOL were estimated in two different
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24 230 models, where both raw and adjusted analyses were conducted including gender, age, marital status,
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26 231 ethnicity, educational level and region as covariates. In case of no convergence in the model,
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28 232 selected covariates were omitted. In the second step the ratio of change in health care costs to
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31 233 change in QOL were calculated.
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36
37 235 There is no official threshold for willingness-to-pay in Denmark and we compared the health care
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39 236 cost per QALY to predefined willingness-to-pay thresholds of a cost-effective treatment defined by
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42 237 the National Institute for Health and Care Excellence (NICE) at 22,804€ (20,000£) per QALY,[25]
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44 238 and the widely used threshold of 43,979€ (50,000 USD) per QALY,[26]. To explore if adherence to
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46 239 the exercise therapy component had an impact on the results, a sub-analysis repeating all analyses
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49 240 restricted to patients with high compliance was conducted. All analyses were reported separately for
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51 241 knee and hip patients.
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4 243 As previously proposed for cost-effectiveness studies and clinical trials in OA,[27,28] missing
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6 244 values for the EQ-5D index score at follow up were imputed using Multiple Imputations (MI) with
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9 245 chained equations under the assumption of data being missing at random,[29]. Since EQ-5D was
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11 246 not normal distributed, Predictive Mean Matching was applied, and all baseline variables presented
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13 247 in the study and outcome variables of interest were included in the model. In total, 40 datasets were
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16 248 generated, approximately equal to the largest percentages of missing observations for the outcome
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18 249 as recommended,[30].

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23 251 Since costs for health care services delivered in municipal settings were not available, all analyses
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25 252 were repeated stratified for patients attending GLA:D® in private physiotherapy clinics vs. in
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27 253 municipal rehabilitation centers. To explore the impact of missing data, a sensitivity analysis
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30 254 repeating all analyses restricted to complete cases was conducted and all analyses were repeated
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32 255 excluding patients who died during follow up.

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36 257 The significance level for all statistical analyses was defined a priori at $p < 0.05$. All analyses were
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39 258 performed using the SAS 9.4 (SAS Institute, North Carolina, USA).

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45 260 **RESULTS**

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52 262 12,162 knee patients and 4,093 hip patients were included in the study and follow up data on EQ-
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54 263 5D were available for 77% immediately after treatment and 61% at one year (Figure 1). Patients
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57 264 with complete information had slightly better, but most likely not clinically relevant better health
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59 265 status at baseline compared to patients with incomplete information (Table S1, Supplementary
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4 266 Appendix). Baseline characteristics are presented in Table 1. Three quarters of the patients were
5
6 267 female, median symptom duration was 2 years, almost two thirds reported use of pain medication
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9 268 and 31% and 4% of knee and hip patients, respectively, reported previous surgery in most affected
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11 269 joint. Seven percent and 17% of knee and hip patients, respectively, reported to have had a joint
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13 270 replacement surgery between start intervention and the 12 m follow up measurement.
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19 272 [Figure 1]
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22 273 [Table 1]
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28 275 Adjusted health care costs and costs for home care one year prior to and three years after entering
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30 276 the intervention are presented in Figure 2a-e, adjusted public transfer payments are presented in
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32 Table 2 and mean public transfer payments are presented in Table S2, Supplementary Appendix.
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35 278 Additionally, mean and adjusted costs one year prior to and one/three years after entering the
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37 279 intervention respectively are presented in Table S3 and S4, Supplementary Appendix. To take the
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39 potential influence of covariates into account, costs are estimated for average patients, i.e. women,
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42 281 65 years old, married/co-living, ethnic Danish, low educational level and living in the Capital
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44 282 Region. Public transfer payments are estimated for women, 55 years old, married/co-living, ethnic
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46 283 Danish, low educational level and living in the Capital Region since the population was restricted to
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48 adults under the age of retirement in this analysis, as public transfer payments target this age group.
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51 285 In the one-year horizon, monthly adjusted health care costs for knee and hip patients were 263€ and
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53 286 235€ one year prior to the intervention, rising to 331€ and 397€ the year after entering the program
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55 (Table S4, Supplementary Appendix). In the three-year horizon, yearly adjusted health care costs
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58 288 one year prior to the intervention were 3,392€ and 3,051€ for knee and hip patients, rising to 4,128€
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4 289 and 4,473€ the third year after entering the intervention, observing the highest costs the second year
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7 290 post-intervention for knee patients and the first year post-intervention for hip patients (Figure 2a).
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9 291 The increase in mean health care costs was mainly due to costs related to surgeries in the knee or
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11 292 hip which the first year after index date in the adjusted analysis accounted for 46€/month of an
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13 293 increase in costs of 68€/month in knee patients and 130.8€/month of an increase in costs of
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16 294 162.8€/month in hip patients (Table S4, Supplementary Appendix). On average, the raw EQ-5D
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18 295 score increased from 0.711 to 0.756 points for knee patients and from 0.705 to 0.747 for hip
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20 296 patients from baseline to one year follow up (Table 3).

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29 299 [Table 2]

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32 300 [Table 3]

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38 302 Adjusted change in health care cost from the year prior to entering GLA:D® to the year after
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40 303 entering GLA:D® was 298€ (95% CI: 206-419) and 640€ (95% CI: 400-1,009) and QALYs gained
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42 304 were 0.035 (95% CI: 0.033-0.037) and 0.028 (95% CI: 0.025-0.032) for knee and hip patients,
43
44 305 respectively. Hence, one-year estimated adjusted health care costs was 8,497€ (95% CI: 6,242-
45
46 306 11,324) for knee patients and 22,568€ (95% CI: 16,000-31,531) for hip patients per QALY gained
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48 307 (Table 4). Restricting the regression analysis to patients with high compliance, the one-year
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50 308 adjusted health care costs per QALY gained was lower compared to all patients; 5,438€ (95% CI:
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52 309 2,758-9,231) for knee patients and 17,330€ (95% CI: 10,041-29,364) for hip patients primarily due
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54 310 to lower change in health care costs (Table 4). Although the upper limit of the 95% CI for hip
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56 311 patients was in between the two predefined willingness-to-pay thresholds, the estimated health care
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4 312 costs per QALY for both knee and hip patients were below both of the two predefined willingness-
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7 313 to-pay thresholds.
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18 317 Sensitivity analyses showed that knee and hip patients attending GLA:D® in a private clinic had
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21 318 similar health care costs per QALY but that patients attending GLA:D® in a municipal setting had
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23 319 higher costs for knee patients and lower costs for hip patients compared to all patients. This
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25 320 difference was primarily explained by different change in health care costs (Table S5,
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27
28 321 Supplementary Appendix). The complete case analysis showed lower change in health care costs
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30 322 and lower health care costs per QALY for knee patients (4,829€ (95% CI: 2,313-8,378)) but for hip
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32 323 patients the ratio was similar to that of all patients (Table S5, Supplementary Appendix). 53 patients
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34 324 died within the one-year follow up period and 11 of these within the first 3 months. Repeating all
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37 325 analyses excluding deaths in the regression analyses showed results similar to the main analysis
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39 326 (data not shown).
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43 44 45 46 328 **DISCUSSION** 47 48 49 50 329

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52 330 Our study demonstrated that an 8-week supervised patient education and exercise therapy program
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55 331 for knee or hip OA implemented in primary care is cost-effective in a one-year horizon with health
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57 332 care costs of 8,497€ per QALY for knee patients and 22,568€ for hip patients who signed up for the
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333 intervention. Despite the physiotherapy visits needed to participate in the GLA:D[®] program,
334 increased health care costs were primarily related to knee or hip surgeries (accounting for 70 and
335 80% of the increased costs, respectively) and although the mean absolute change in health related
336 QOL is relatively low (~0.03) the intervention is still considered cost-effective. These results
337 support large scale implementation of GLA:D[®] in clinical practice.

338
339 To our knowledge this is the first study evaluating the cost-effectiveness of a combined supervised
340 OA education and exercise therapy program with widespread implementation in primary care.
341 Previous analyses of the GLA:D[®] program, but with twice the number of supervised neuromuscular
342 exercise sessions, weight loss, insoles and pain medication if needed, have found similar
343 results,[15,31]. A model-based study suggested that exercise therapy and education was cost-
344 effective as compared to usual care for patients with knee or hip OA in Canada[31], while an
345 analysis of results from a randomized trial comparing supervised exercise therapy, education and
346 other recommended non-surgical interventions to written advice in patients with moderate to severe
347 knee OA found the intervention to be cost-effective with incremental cost effectiveness ratios of
348 6,229 to 20,688 €/QALY,[15]. Even though our study is a pre-post study and therefore not directly
349 comparable our findings are also in line with other previous studies which have indicated that
350 supervised exercise therapy alone as treatment for OA is cost-effective. Three randomized trials
351 demonstrated that supervised exercise therapy in addition to usual care, supplementary class-based
352 exercise in addition to a home-based program and supervised exercise therapy compared to general
353 practitioner care alone was likely to be cost-effective in people with knee and/or hip OA,[32-34].
354 Also, a model-based study estimated that adding the combination of diet and exercise therapy to
355 usual care for overweight and obese patients with knee OA was cost-effective,[35]. Our study adds

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4 356 to this body of evidence, that large-scale implementation in clinical practice of a structured
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6 357 combined supervised education and exercise therapy program seems cost-effective in a one-year
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15 360 In this study, the increased health care costs both one and three years after entering the GLA:D®
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18 361 program were primarily related to surgeries in the knee or hip. According to a stepwise treatment
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20 362 approach, joint replacement surgery is considered to be relevant in patients with end-stage OA once
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23 363 all appropriate non-surgical treatment options such as patient education and supervised exercise
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25 364 therapy of sufficient dose and length, weight loss, walking aids and pain medication have failed to
26
27 365 reduce symptoms sufficiently,[36,37]. Existing evidence indicates that providing supervised
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30 366 exercise therapy can have positive impact on the number of patients having joint replacement
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32 367 surgery,[38-40], time to surgery,[39,40] and outcomes from surgery[41]. Ackerman et al conducted
33
34 368 a budget impact analysis of implementing a first-line management program such as GLA:D® in
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36 369 Australia and demonstrated that if total knee replacement was avoided in only 1 in 12 GLA:D®
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39 370 participants, the program would generate cost savings in the Australian health care system,[42].
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41 371 Although the lack of control group in the current study precludes analyses of avoidance of joint
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43 372 replacements, it highlights that regardless of surgery during follow up, supervised education and
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46 373 exercise therapy is cost-effective.

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52 375 As a result of similar change in EQ-5D, but lower change in health care costs, health care costs per
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54 376 QALY were lower in patients compliant to the intervention (i.e. attending at least 10 supervised
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57 377 exercise sessions) compared to all patients enrolled in the program, indicating that the dosage of
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59 378 exercise therapy is important. Although we did not find that higher compliance was associated with
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4 379 greater effects on the EQ-5D, the lower change in health care costs in the compliant patients
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7 380 underlines the importance of exercise dosage as suggested by a systematic review and meta-
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9 381 regression analysis of 48 randomized controlled trials in patients with knee OA showing that 12 or
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11 382 more supervised exercise sessions are more effective than fewer supervised sessions,[43], and a
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13 383 systematic review and meta-analysis in patients with hip OA showing that supervised exercise
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15 384 therapy with high compliance with dose recommendations compared to uncertain compliance
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18 385 (studies where compliance was not possible to categorize according to recommendations) was more
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20 386 effective,[44]. Although dosage seems important for the effect and cost-effectiveness, knowledge of
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23 387 optimal exercise dosage in OA is still lacking,[9,43,45].
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29 389 As there is no official threshold defining a cost-effective treatment in Denmark, we compared the
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31 390 health care costs per QALY to two different internationally widely used willingness-to-pay
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33 391 thresholds. Although the estimated health care costs per QALY for both knee and hip patients were
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35 392 below both of the two thresholds, the upper limit of the 95% CI for hip patients was in between the
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38 393 two thresholds, thus we cannot rule out that the true health care costs per QALY for hip patients is
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40 394 above the lower willingness-to-pay threshold (22,804€). A threshold value for willingness-to-pay
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42 395 for improvements in health is arbitrary and depending on the context such as budget and other
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44 396 treatment options,[26]. Country-level threshold value based on GDP per capita has been discussed
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47 397 but remains unsettled,[46]. When deciding which treatment options to implement and offer, the
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49 398 results from this study can support clinicians and decision-makers in terms of one-year cost-
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51 399 effectiveness of supervised education and exercise therapy implemented nationwide for patients
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53 400 with knee and hip OA in clinical practice.
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402 **Strengths and limitations**

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

411

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

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

431
432 Only around 60% of the costs covering the program for most patients attending GLA:D[®] in private
433 physiotherapy clinics were taken into account in the analyses i.e. patients out-of-pocket costs and
434 costs covering the program in municipal settings as well as medications bought over the counter
435 were not included. As the increase in costs in the primary health care sector and in costs covering
436 medications the first year following index date only constitute a very low proportion of the
437 increased costs in total, this limitation is not considered to substantially affect the overall results.

438
439 There was a loss to follow up in the GLA:D[®] registry and conducting a sensitivity analysis
440 restricted to patients with complete information revealed that they had less mean change in health
441 care costs than all included patients, indicating a risk of selective loss to follow up in the GLA:D[®]
442 registry, however, the evaluation on health care costs per QALY included all patients enrolled in
443 GLA:D[®], imputing the missing outcome values at follow up. Imputing missing outcome values
444 relied on the assumption that data were missing at random, i.e. the missingness was related to
445 variables included in the model. However, there is a risk that loss to follow up was related to
446 unobserved factors not available for the analysis (e.g. good or bad outcome from the GLA:D[®]
447 program). One third did not provide information on compliance and there is a risk that lower change

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

454
455 The current study is based on real-world outcome data collected in nationwide physiotherapy clinics
456 and actual health care costs retrieved from national registries, supporting the generalizability of the
457 results. However, patients attending GLA:D[®] are a preselected group of patients who are commonly
458 referred to physiotherapy for their symptoms with most being able to pay partly for the intervention,
459 which might limit the generalizability.

461 CONCLUSIONS

462
463 A structured 8-week supervised education and exercise therapy program delivered in physiotherapy
464 practice was cost-effective at one year in patients with knee and hip OA compared to conventional
465 willingness-to-pay thresholds except the upper limit of the 95% CI for hip patients which was in
466 between two thresholds. Both health-related QOL and health care costs increased during the one-
467 year time horizon, the latter mainly due to knee or hip surgeries. The results support large scale
468 implementation of a structured supervised evidence-based patient education and exercise therapy
469 program targeting patients with knee or hip OA and can guide clinicians and decision makers on
470 what to expect when such programs are implemented in clinical practice.

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471 **ACKNOWLEDGMENTS**

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473 The authors would like to thank the clinicians and patients involved in collecting data for GLA:D®.

474

475 **PATIENT AND PUBLIC INVOLVEMENT STATEMENT**

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

478

479 **DATA SHARING STATEMENT**

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

484

485 **AUTHOR CONTRIBUTIONS**

486

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

488 Acquisition of data: DTG, ER, STS

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

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4 490 Drafting the article: DTG, STS
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7 491 Revising the article critically for important intellectual content: DTG, ER, RI, JK, STS
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10 492 Final approval of the article: DTG, ER, RI, JK, STS
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13 493 Obtaining of funding: STS
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20 495 **ROLE OF THE FUNDING SOURCE** 21 22 23

24 496
25
26
27 497 This work was supported by the Danish Rheumatism Association and the Physiotherapy Practice
28
29
30 498 Foundation. Grant numbers not applicable.
31

32
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34
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36
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44
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46
47
48 505 innovation program (grant agreement No 801790).
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54 507 None of the funding sources had any role in the study other than to provide funding.
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509 **CONFLICT OF INTEREST**

510

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

516

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

520

521 R Ibsen: None

522

523 J Kjellberg: None

524

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

526

527 **Ethics Statement**

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

For peer review only

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4 **TABLE LEGENDS**
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8 696 Table 1. Baseline characteristics in knee and hip patients attending GLA:D®
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11 697 Table 2. Adjusted public transfer payments one year prior to and one or three years following
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13 698 GLA:D® for knee and hip patients
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16 699 Table 3. Change in health-related quality of life from baseline to 12 months for knee and hip
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18 700 patients attending GLA:D®
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21 701 Table 4. Adjusted and raw estimated health care costs per QALY from baseline to 12 months for all
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23 702 knee and hip patients attending GLA:D® and for knee and hip patients with high compliance
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704 **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)

705 Missing values: BMI n: 5 (knee), n: 7 (hip); Number of comorbidities n: 711 (knee), n: 215 (hip); Symptom duration
706 (mainly missing due to technical problems): n: 3,157 (knee), n: 1,096 (hip) ; Pain intensity: n:23 (knee), n:9 (hip) ;
707 Bilateral symptoms: n:32 (knee), n:20 (hip) ; Walk speed: n:610 (knee), n:221 (hip); KOOS/HOOS QOL: n: 36 (knee),

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708 n: 21 (hip).

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

710 □Self-reported use of pain medication during last 3 months

711 %Number of comorbidities calculated from self-report of the following conditions: hypertension, cardiovascular
712 diseases, lung diseases, diabetes, stomach diseases, liver- or kidney diseases, blood diseases, cancer, depression,
713 rheumatoid arthritis, neurological disorders, other medical diseases

714 &Self-reported previous surgery in worst joint

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

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717 **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	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	0.344	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	0.977	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	0.205	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	0.607	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	0.577	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	0.999	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	0.100	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	0.377	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	0.600	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	0.523	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	0.521	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

718 [#]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
719 Capital Region estimated using a generalized estimating equation gamma regression model for repeated measures including sex, age, marital status, ethnicity,
720 education and region as covariates. Because of no convergence in the model following covariates were omitted: 'Early retirement': sex, marital status, ethnicity,
721 education and region; 'Rehabilitation': age, marital status, ethnicity and education; 'Education': age, marital status, ethnicity and education. Adjusted weeks receiving
722 public transfer payments in three-year horizon for women, 55 years and low education estimated using a generalized estimating equation gamma regression model for
723 repeated measures including sex, age and education as covariates. Because of no convergence in the model following covariates were omitted: 'Sheltered
724 employment': sex and education; 'Disability pension': sex and education; 'Early retirement': age.

725 [§]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
726 Capital Region estimated using a generalized estimating equation gamma regression model for repeated measures including sex, age, marital status, ethnicity,
727 education and region as covariates. Because of no convergence in the model following covariates were omitted: 'Early retirement': sex, marital status, ethnicity,
728 education and region; 'Rehabilitation': age, marital status, ethnicity, education and region; 'Education': age, marital status, ethnicity, education and region. Adjusted
729 weeks receiving public transfer payments in three-year horizon for women, 55 years and low education estimated using a generalized estimating equation gamma
730 regression model for repeated measures including sex, age and education as covariates. Because of no convergence in the model following covariates were omitted:

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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.

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733 **Table 3. Change in health-related quality of life from baseline to 12 months for knee and hip**
734 **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

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

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

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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

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745 **FIGURE LEGENDS**

746 Figure 1. Flow chart

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

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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

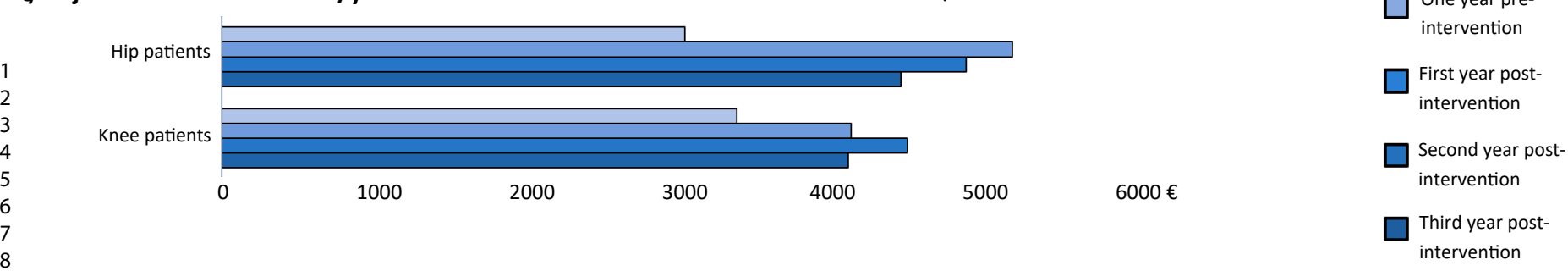
6,990 knee patients had complete information on EQ-5D

2,349 hip patients had complete information on EQ-5D

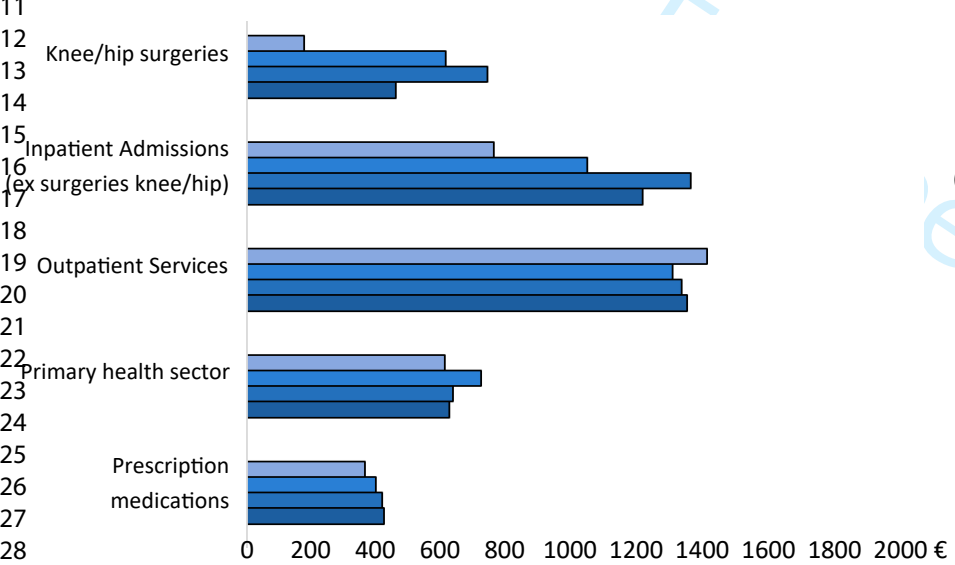


a) Adjusted health care costs/year - total

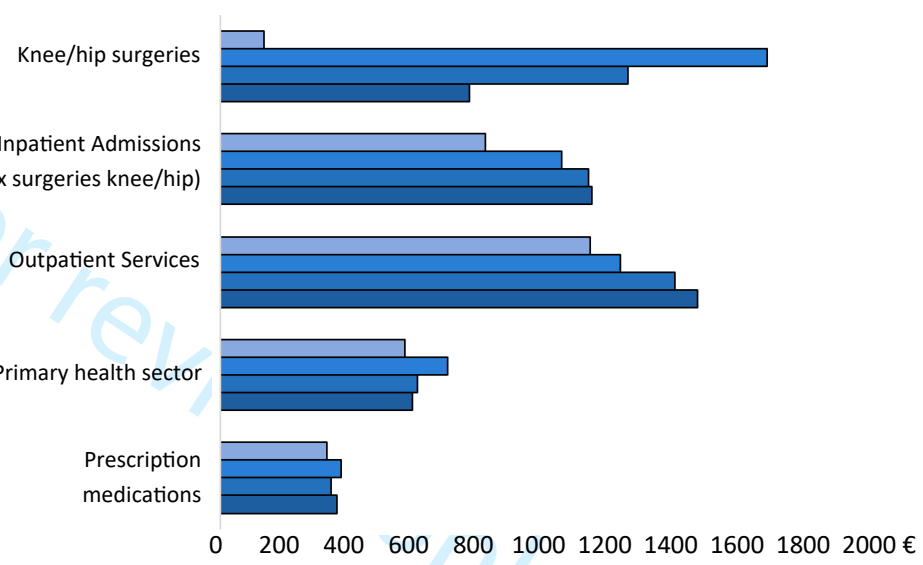
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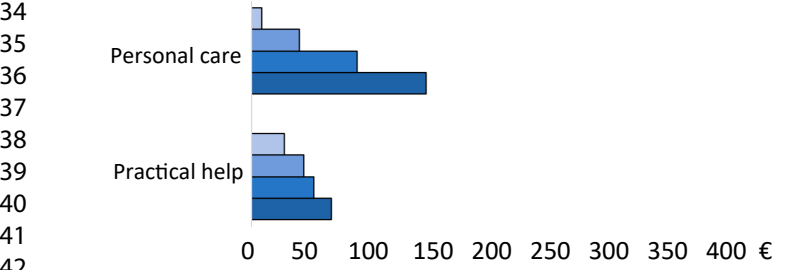
b) Adjusted health care costs/year - knee patients



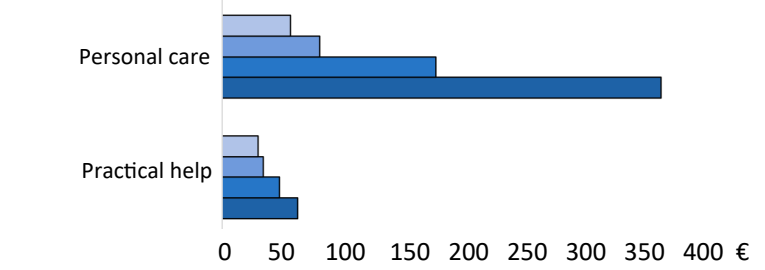
c) Adjusted health care costs/year - hip patients



d) Adjusted costs/year home care - knee patients



e) Adjusted costs/year home care - hip patients



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

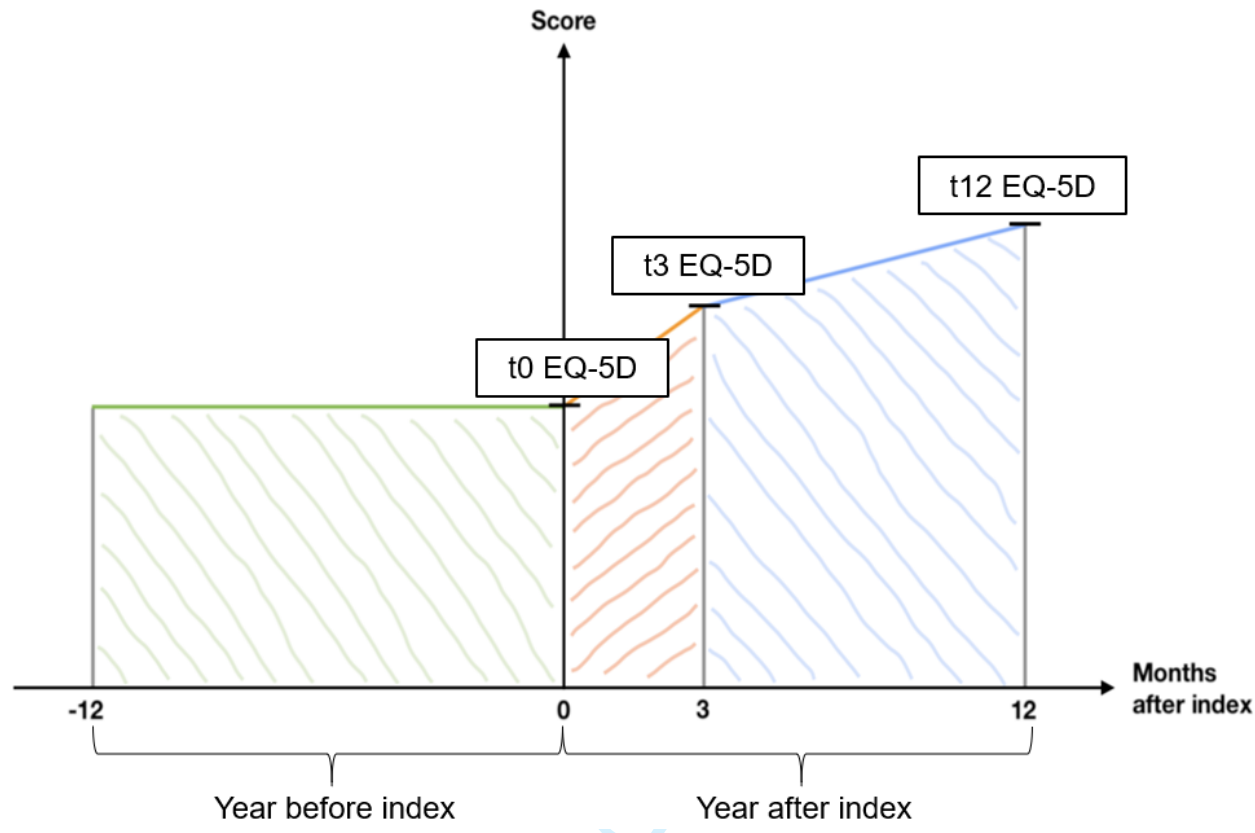
Table S2: Mean public transfer payments one year prior to and one or three years following GLA:D[®] for knee and hip patients

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

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



16

17 **Table S1: Baseline characteristics in patients with complete information and patients who had**
 18 **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 leave¹, % (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 comorbidities², % (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)

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4	Previous surgery in worst joint^{&}, % (n)	30.2 (2,112)	3.2 (78)	31.3 (1,619)	4.8 (84)
5	Receive home care, % (n)	8.9 (621)	9.6 (224)	11.5 (593)	12.4 (215)
6	Use of pain medication^o (yes), % (n)				
7	Overall	60.9 (4,256)	62.7 (1,473)	61.8 (3,196)	66.1 (1,156)
8	Paracetamol	49.5 (3,463)	52.9 (1,243)	50.5 (2,610)	53.8 (941)
9	NSAIDs	35.8 (2,504)	32.5 (764)	35.2 (1,182)	37.5 (655)
10	Opioids	6.6 (459)	8.1 (190)	7.9 (409)	10.1 (177)
11	KOOS/HOOS QOL[*] (0-100, best to worst), mean	46.0 (14.5)	47.9 (15.0)	44.1 (15.0)	46.7 (15.3)
12	(SD)				

19 Missing values: BMI: n: 2 (knee, complete), n: 5 (hip, complete), n: 3 (knee, incomplete), n: 2 (hip, incomplete); Ethnic background: n: 1 (hip,
20 complete), n: 2 (knee, incomplete); Social status: n: 72 (knee, complete), n: 19 (hip, complete), n: 107 (knee, incomplete), n: 29 (hip, incomplete);
21 Sick leave: n: 6 (knee, complete), n: 1 (hip, complete), n: 19 (knee, incomplete), n: 3 (hip, incomplete); Number of comorbidities: n: 412 (knee,
22 complete), n: 132 (hip, complete), n: 299 (knee, incomplete), n: 83 (hip, incomplete); Symptom duration (mainly missing due to technical problems):
23 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
24 (hip, complete), n: 15 (knee, incomplete), n: 6 (hip, incomplete); Bilateral symptoms: n: 14 (knee, complete), n: 10 (hip, complete), n: 18 (knee,
25 incomplete), n: 10 (hip, incomplete); Walk speed: n: 309 (knee, complete), n: 100 (hip, complete), n: 301 (knee, incomplete), n: 121 (hip,
26 incomplete); Receive home care: n: 31 (knee, complete), n: 8 (hip, complete), n: 36 (knee, incomplete), n: 8 (hip, incomplete); KOOS/HOOS QOL: n:
27 17 (knee, complete), n: 9 (hip, complete), n: 19 (knee, incomplete), n: 10 (hip, incomplete).

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

29 ^oSelf-reported use of pain medication during last 3 months

30 ^lSelf-reported sick leave for more than 1 month during last year due to knee/hip

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

33 [&]Self-reported previous surgery in worst joint

34 ^{*}Knee injury and Osteoarthritis Outcome Score or Hip disability or Osteoarthritis Outcome Score Quality Of Life sub-scale score

35 **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/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	0.000	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	0.000	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	0.000	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	0.000	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	0.000	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	0.000	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	0.000	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	0.000	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		

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37 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	Post-period		Post-period		Post-period		Pre-period	Post-period		Post-period		Post-period		
	(1 year)	(mth 1-3)	p-value	(mth 4-12)	p-value	(1 year)	p-value	(1 year)	(year 1)	p-value	(year 2)	p-value	(year 3)	p-value	
	Cost	Cost		Cost		Cost		Cost	Cost		Cost		Cost		
	(€/month)	(€/month)		(€/month)		(€/month)		(€/Year)	(€/year)		(€/year)		(€/year)		
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 LA: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	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		

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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
39	*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													
40	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													
41	ethnicity were omitted estimating costs for home care.													
42	§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													
43	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.													
44	¶Surgery is not predicted in a three-year horizon because of no convergence of the model.													

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46 **Table S5. Sensitivity analysis - adjusted estimated health care cost per QALY from baseline to 12**
 47 **months for knee and hip patients attending GLA:D® in private clinics, municipal clinics and patients**
 48 **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 (181-385)	0.036 (0.033-0.038)	7,464 (5,485-10,132)	651 (398-1,050)	0.028 (0.024-0.033)	22,914 (16,583-31,818)
Municipal clinic[#]	396 (118-949)	0.032 (0.026-0.039)	12,292 (4,538-24,333)	443 (69-2,056)	0.028 (0.017-0.043)	15,550 (4,059-47,814)
Complete cases[‡]	167 (74-310)	0.035 (0.032-0.037)	4,829 (2,313-8,378)	579 (284-1,142)	0.027 (0.023-0.032)	21,067 (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	<i>Single study-based estimates:</i> 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	<i>Synthesis-based estimates:</i> 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	<i>Single study-based economic evaluation:</i> 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	<i>Model-based economic evaluation:</i> 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	<i>Single study-based economic evaluation:</i> 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	<i>Model-based economic evaluation:</i> 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

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