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Understanding the role of diabetes in the osteoarthritis disease and treatment process: The Swedish Osteoarthritis and Diabetes (SOAD) cohort

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3 **1 Understanding the role of diabetes in the osteoarthritis disease and treatment**
4 **process: The Swedish Osteoarthritis and Diabetes (SOAD) cohort**
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51 26 Keywords: Osteoarthritis, diabetes, register, cohort, exercise, surgery.

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2
3 29 **ABSTRACT** (298 words)
4

5 30 **Introduction**
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7
8 31 Osteoarthritis (OA) is the most common form of arthritis and a leading cause of disability worldwide.
9
10 32 Metabolic comorbidities such as type 2 diabetes occur with a higher rate in people with OA than in the
11
12 33 general population. Several factors including obesity, hyperglycemia toxicity and physical inactivity have
13
14 34 been suggested as potential links between diabetes and OA, and have been shown to negatively impact
15
16 35 on patients' health and quality of life. However, little is known on the role of diabetes in determining the
17
18 36 outcome of non-surgical and surgical management of OA, and at the same time, how different OA
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20 37 interventions may affect diabetes control. Thus, the overall aim of this project is to explore (1) the impact
21
22 38 of diabetes on the outcome of non-surgical and surgical OA treatments, and (2) the impact of non-surgical
23
24 39 and surgical OA treatments on diabetes control.

25 40 **Methods and analysis**

26 41 The study cohort is based on prospectively ascertained register data on a national level in Sweden. Data
27
28 42 from OA patients who received a first-line non-surgical intervention and are registered in the National
29
30 43 Quality Register for Better Management of Patients with Osteoarthritis will be merged with data from the
31
32 44 Swedish Knee and Hip Arthroplasty Registers and the National Diabetes Register. Additional variables
33
34 45 regarding patients' use of prescribed drugs, comorbidities, socioeconomic status, and cause of death will
35
36 46 be obtained through other national health and population data registers. We will thus create a cohort
37
38 47 that will allow us to follow OA patients presenting to health care through their entire care process. The
39
40 48 linkage will be performed on an individual level using unique personal identity numbers.

41 49 **Ethics and dissemination**

42 50 This study received ethical approval (2019-02570). Results from this cohort will be submitted to peer-
43
44 51 reviewed scientific journals and reported at the leading national and international meetings in the field.
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3 53 **ARTICLE SUMMARY**
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5 54 **Strengths and limitations of this study**
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- 8 55 • This study will use a large nationwide population-based cohort based on data from national
9 56 quality registers with high coverage and completeness to explore the relationship between
10 57 diabetes and osteoarthritis (OA) and their related care process.
 - 11 58 • We will include data regarding both non-surgical and surgical treatments for patients with OA
12 59 giving the possibility to capture the influence of diabetes across the whole spectrum of OA
13 60 treatments.
 - 14 61 • We will include covariate information from several national registers that will allow to account
15 62 for potential confounders and effect modifiers.
 - 16 63 • A limitation of register-based studies is that the variables available and the characteristics of the
17 64 treatments provided are predetermined, i.e., it is not possible to add covariates, exposures or
18 65 outcomes (not in the registers) or to modify the interventions that have been given.
 - 19 66 • People included in the BOA, SHPR and SKAR registers received an intervention due to OA. Certain
20 67 treatments are given to patients with specific characteristics, which implies that selection bias
21 68 and confounding by indication may bias our estimates.
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70 INTRODUCTION

71 Osteoarthritis (OA) is the most common form of arthritis [1]. In Sweden, more than 25% of the population
72 aged >45 years is estimated to suffer from OA related pain symptoms and associated physical activity
73 restrictions [2]. The average annual cost for a person affected by OA is reported to exceed €2,000, while
74 the total European expense directly attributable to OA is estimated to be as high as €700 billion [3].

75 In addition to the already huge health and societal burden of OA, recent studies suggest that OA patients
76 are twice as likely to have comorbidities compared to controls of the same age, indicating that the co-
77 occurrence of multiple conditions in OA patients is the norm rather than the exception [4]. For instance,
78 based on data showing a higher incidence of OA in overweight patients with metabolic disorders, a
79 metabolic OA phenotype has been hypothesised [5-7]. Among the metabolic disorders, diabetes seems
80 to play a central role due to its high prevalence and the toxic effect that hyperglycaemia has on the
81 cartilage and its cells, and to the motor and sensory system through peripheral neuropathy [8-10].

82 According to data from the Swedish National Diabetes Register (NDR), approximately 5% of the Swedish
83 population has diabetes, with type 2 diabetes accounting for approximately 90% of the cases[11]. Persons
84 with diabetes have a higher risk of developing cardiovascular diseases and have a 2- to 5-fold increased
85 risk of mortality compared with the general population [12].

86 In OA patients the prevalence of diabetes has been reported to be nearly three times higher than in the
87 general population [7]. Obesity is a shared risk factor for OA and diabetes and can partially explain the
88 association between these diseases [13, 14]. In addition to the mechanical overload caused by the excess
89 weight, adipocytes release cytokines into the bloodstream promoting chronic low-grade inflammation
90 and activating proteolytic enzymes which can trigger matrix degradation and initiate OA. At the same
91 time, adipose-induced low-grade inflammation influences the metabolic dysregulation underlying several
92 metabolic disorders among others, diabetes type II [14].

93 Once diabetes is initiated, it further promotes cartilage degeneration and joint inflammation causing
94 enrichment of advanced glycation endproducts (AGEs) and matrix stiffening preventing optimal
95 cushioning of the joint [7, 15]. This process leads to a worsening in OA symptoms promoting physical
96 inactivity and weight gain and creating a vicious cycle which maintains the metabolic dysregulation and
97 increases joint symptoms [13, 16-18].

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3 98 The evidence-based first-line management for people with OA includes education and exercise, which are
4 99 recommended regardless of OA disease severity [19]. Metabolic comorbidities may have a significant
5 100 impact on the treatment, partially explaining the lack of response experienced by some patients.
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9 101 Replacement of the knee and of the hip is an effective treatment for patients with severe OA who do not
10 102 sufficiently improve after non-surgical management [20]. Due to the rising prevalence of OA and the
11 103 growing demand for this procedure, the number of hip and knee replacements has dramatically increased.
12 104 In Sweden (total population 10 million), 14,700 primary total hip replacements (THRs) and nearly 14,000
13 105 total knee replacements (TKRs) were performed in 2017 with OA as indication. These figures account for
14 106 81% and 97% of the annual hip and knee replacements respectively, and translates in an annual incidence
15 107 of nearly 150 procedures per 100,000 persons for both THR and TKR [21, 22].
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21 108 Considering the association between diabetes and OA, surprisingly little is known regarding the influence
22 109 that diabetes has on the outcome of OA treatments (both non-surgical and surgical) [23, 24]. In addition,
23 110 no evidence exists regarding the effect that OA treatments (both non-surgical and surgical) may have on
24 111 diabetes control. Thus, merging data from multiple Swedish registers will allow us to follow patients with
25 112 OA through the progress of their disease to understand how diabetes influences the OA disease process.
26 113 This study cohort is created to increase knowledge of the influence that diabetes has on the outcomes of
27 114 OA patients who have received non-surgical and/or surgical treatments for hip and knee OA, and the
28 115 influence OA and its treatments have on the diabetes control.
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35 116 **METHODS AND ANALYSIS**

36 117 **Research questions**

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38 118 In order to understand how the coexistence of OA and diabetes influences the treatment effects in these
39 119 diseases, a series of research questions have been posed. The research questions cover two main thematic
40 120 areas: (1) the impact of diabetes on the outcome of non-surgical and surgical OA treatments, and (2) the
41 121 impact of OA non-surgical and surgical OA treatments on diabetes control.
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47 122 Area 1

- 48 123 1. What is the prevalence of diabetes in people with OA undergoing a non-surgical intervention?
- 49 124 2. Is the presence of diabetes, diabetes-related factors (e.g. type of diabetes, diabetes-related
50 125 medication, blood pressure, HbA1c) associated with OA severity (e.g. pain intensity, pain
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3 126 frequency, walking difficulties) of people with OA undergoing a self-management non-surgical
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5 127 intervention?
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7 128 3. Is the presence of diabetes and diabetes-related factors associated with the outcomes of a self-
8
9 129 management non-surgical intervention for people with OA (e.g. change in pain levels, pain
10
11 130 frequency, walking difficulties)?
12
13 131 4. Is the presence of diabetes and diabetes-related factors associated with the risk of joint
14
15 132 replacement in people with OA who underwent a self-management non-surgical intervention?
16
17 133 5. What is the incidence of reoperations and other adverse events such as thromboembolism,
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19 134 cardiovascular events and mortality following primary total hip or knee replacement due to OA in
20
21 135 people with or without diabetes?
22
23 136 6. What diabetes-related factors are associated with the risk of reoperation and other adverse
24
25 137 events following primary total hip or knee replacement among person with diabetes?

24 138 Area 2

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27 139 7. How does a self-management non-surgical intervention for OA influence diabetes control (e.g.
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29 140 change in diabetes drug intake, change in Hb A1c levels) compared to comparable people with
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31 141 diabetes who had not taken part in the intervention?
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33 142 8. How does primary total hip or knee replacement influence the diabetes control compared to
34
35 143 comparable persons with diabetes but with no history of hip or knee arthroplasty?
36
37 144 9. What diabetes-related risk factors are associated with diabetes control following primary total
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39 145 hip or knee replacement due to OA?

39 146 **Main exposures and outcomes**

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41 147 The exposure and outcome measures are described in table 5. Potential confounding factors for main
42
43 148 analysis and disease sub analysis are described with examples.

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45 149 INSERT TABLE 5 HERE

48 150 **The Swedish OA and Diabetes cohort (SOAD)**

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50 151 This nationwide observational study cohort (SOAD) will be based on prospectively obtained individual-
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52 152 level data from four main sources: the National Quality Register for Better Management of Patients with
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54 153 Osteoarthritis (BOA) Register, the Swedish Hip Arthroplasty Register (SHAR), the Swedish Knee
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56 154 Arthroplasty Register (SKAR), and the Swedish National Diabetes Register (NDR). Data starting from the

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3 155 year of each register establishment will be merged using the unique personal identity number (PIN) issued
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5 156 to all legal residents in Sweden. Additional variables regarding patients' use of prescribed drugs,
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7 157 comorbidities, cause of death, and socioeconomic information will be obtained through the following
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9 158 population-based registers:

- 10 159 • The Swedish Prescribed Drug Register (SPDR) held by the National Board of Health and Welfare.
- 11 160 • The National Patient Register (NPR) held by the National Board of Health and Welfare; information
12 161 regarding in-hospital diagnoses and outpatient specialist care diagnoses, e.g. interventions,
13 162 adverse events such as thromboembolism or other comorbid conditions.
- 14 163 • Swedish Cancer Register, The National Board of Health and Welfare.
- 15 164 • The Cause of death Register (CODR) held by the National Board of Health and Welfare
- 16 165 • Longitudinal integration database for health insurance and labour market studies (LISA) held by
17 166 Statistics Sweden for data such as marital status, educational level and country of origin.

18 167 **Data sources**

19 168 BOA: The BOA register was started in 2008 and currently includes more than 100,000 individuals with OA
20 169 of the knee or of the hip who have registered for an evidence-based self-management programme. These
21 170 patients sought treatment for knee and/or hip pain in primary healthcare in Sweden and were referred
22 171 for standardised core treatment (education and supervised exercises) after a confirmed
23 172 clinical/radiographic OA diagnosis in accordance with the recommendations for OA diagnosis from the
24 173 Swedish National Board of Health and Welfare[25]. These guidelines are in line with internationally
25 174 accepted diagnostic criteria, and according to the guidelines, radiographic examination should only be
26 175 used in uncertain cases, if the patient is not responding to treatment or when a surgical intervention is
27 176 planned [26, 27]. BOA offers all the patients two education sessions focusing on the pathophysiology of
28 177 OA and the benefit of exercise. A face-to-face session with a physiotherapist is also offered. In this session,
29 178 the patients receive a personalised intervention programme and the necessary instructions to perform it
30 179 independently at home. In addition, BOA offers patients the possibility to undertake up to 12 supervised
31 180 group exercise session with a physical therapist. Thus, the register contains two separate cohorts that
32 181 performed, in addition to the education sessions, either home exercise or supervised exercise. The
33 182 register has a data completeness of almost 90% and the BOA participants have answered validated and
34 183 patient-relevant socio-demographic and outcome questionnaires after the interventions (2-5 months) and
35 184 at 1 year (12-15 months) (Table 1).

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3 185 INSERT TABLE 1 HERE
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6 186 SHAR: Started in 1979, SHAR registers primary hip replacement operations and reoperations in Sweden
7
8 187 including individual patient data, surgical technique and type of implant used. Since 2002 patient-reported
9
10 188 measures such as joint pain, HRQoL and satisfaction with treatment have also been collected before
11
12 189 surgery and 1, 6 and 10 years postoperatively. The register encompasses 318 000 primary total hip
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14 190 replacements due to OA and 61 500 reoperations after total hip replacements where OA was the main
15
16 191 reason for the primary surgery (at the end of 2018). The register has an overall data completeness of
17
18 192 98,5% (2016) including all indications for total hip replacements (Table 2).

19 193 SKAR: The Swedish Knee Arthroplasty Register is a Swedish National Quality Register founded in 1975.
20
21 194 The register collects individual patient data, surgical technique and type of implant used for patients who
22
23 195 undergo knee replacement. The SKAR also collects information on re-operations/revision surgery. SKAR
24
25 196 has a completeness of 98.1 % (2016) and have registered almost 270,000 primary knee replacements due
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27 197 to OA and more than 21 400 revisions at the end of 2018 (Table 3).

28 198 INSERT TABLE 2 AND 3 HERE
29

30 199 NDR: NDR has been a Swedish National Quality Register since 1996 and collects data on clinical
31
32 200 characteristics, risk factors, laboratory analyses, complications of diabetes, and medications for patients
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34 201 18 years of age or older with a diagnosis of diabetes (Table 4). The completeness is 96.5 % (2017) and the
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36 202 register has 750 004 (2017) unique individuals in their database. More than 95% of all individuals with
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38 203 type 1 diabetes mellitus (T1DM) and 90% of individuals with type 2 diabetes mellitus (T2DM) in Sweden
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40 204 are included in the NDR.

41 205 INSERT TABLE 4 HERE
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43 206 **Data linkage**

44 207 Personal Identity Number (PIN): In Sweden, all legal residents are registered with a unique PIN that
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46 208 provides information on date of birth and sex. Swedish law requires all documentation regarding
47
48 209 healthcare contacts to be registered using the patient's PIN[28]. The PIN is also used for registration of
49
50 210 data for statistics such as national population-based registers and healthcare quality registers [29, 30].
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52 211 The system allows for linkage of data at an individual level between the different registers in Sweden with
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54 212 the possibility of creating merged research databases for epidemiological research on large populations,
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3 213 after the relevant ethical approval has been obtained. Data linkage for the current study is described in
4 figure 1.
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7 215 INSERT HERE FIGURE 1
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9 216 **Analysis plan**

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12 217 We will develop a specific statistical analysis plan for each specific study that will be conducted within
13 218 SOAD. These will follow a number of general principles. We will aim for inclusion of all available OA and
14 219 diabetes patients to limit potential selection bias. We will use multiple imputation methods to impute the
15 220 missing data on exposures, outcomes and confounders, when relevant. The imputation model will be
16 221 specific for each study and compatible with the chosen analysis model. For example, the fully conditional
17 222 specification (also called chained equations) may be used to enable flexible models for proper imputation
18 223 of all variables. In the statistical modelling we will aim for estimation of causal effects and statistical
19 224 models will be chosen accordingly using direct acyclic graphs (DAGs) to enable proper confounding control
20 225 [31]. For confounding control, we will use regression models or inverse probability weighting. For analysis
21 226 of panel data (i.e. longitudinal repeated measurements of the participants and/or data clustered by
22 227 caregiver) we will use multilevel regression models. For time-to-event data we will use the proportional
23 228 hazards Cox regression model, or, if appropriate, parametric models. For mediation analysis, we will use
24 229 linear models or maximum likelihood structural equation models when appropriate. For categorical
25 230 outcomes we will use other approaches [32, 33]. We will report the results from all analyses as relevant
26 231 estimated effect size (such as risk differences, risk ratios or hazard ratios) with 95% confidence intervals
27 232 and interpret these for clinical relevance, irrespectively of statistical significance [34, 35].
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32 233 Considering the variety of exposures and outcome studied, we have not performed any specific sample
33 234 size analysis. However, we will include all the available data, with ~100,000 BOA participants, whereof an
34 235 estimated 15,000 have diabetes [36]. Regarding the SHAR and SKAR, we will have data for nearly 30,000
35 236 joint replacements. Based on previous studies we expect that the prevalence of diabetes will be around
36 237 8% and 14% among patients undergoing THR and TKR, respectively [37, 38]. We expect that this will enable
37 238 precise estimation of the main effects of interest.
38

39 239 **Patient and public involvement**

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41 240 Patient representatives were not involved in the development of the research question or the design of
42 241 this study. Patients were however involved in the creation of the BOA supported self-management
43 242 programme and contributed with the key content of the programme and the mode of delivery from the
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3 243 patients' perspective [39]. The Swedish Hip and Knee Arthroplasty Registers have patient representatives
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5 244 on their respective steering committees.

6 7 245 **ETHICS AND DISSEMINATION**

8 9 246 **Storage and management of data**

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11 247 A copy of the full data set will be stored at the Center of Registers Västra Götaland, Gothenburg, Sweden.
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13 248 A second copy of the full data set will be stored at Lund University on the platform LUSEC (Lund
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15 249 information security platform). The platforms are designed to securely store, manage and analyse data in
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17 250 accordance with the European Union general data protection regulation (GDPR). The process of linkage,
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19 251 storage and management of data, the role of informed consent in register-based research and
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21 252 safeguarding the integrity of study participants follows the legal and ethical frameworks as described by
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23 253 Swedish law and ethical boards. This has been described by Ludvigsson et al [28].

24 25 254 **Dissemination**

26
27 255 The results from this study will be published in peer-reviewed scientific journals and will be presented at
28
29 256 the leading national and international meetings in the field. The results will also be disseminated through
30
31 257 annual reports published on the registers' websites.

32 33 258 **DISCUSSION**

34
35 259 This study cohort will provide unique insights on the relationships between diabetes and OA. By using
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37 260 data from the BOA, SHAR, SKAR and NDR registers we will be able to investigate the influence of diabetes
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39 261 on the outcome of non-surgical and surgical OA interventions as well as the effect of OA treatments on
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41 262 diabetes control.

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43 263 To our knowledge, this will be the largest dataset combining data on OA and diabetes management.
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45 264 Thanks to the large sample size on national level, results arising from this study will likely have a high
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47 265 external validity and generalisability. However, treatment data collected in national registers are likely to
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49 266 be influenced by the regional differences in treatment protocols and data collection that characterise
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51 267 different clinical environments when compared to e.g. highly standardised clinical trials.

52
53 268 In conclusion, to optimise treatments for OA and diabetes and move towards a personalised-care
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55 269 approach, it is important to identify factors and comorbidities that may negatively influence the outcome
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57 270 of the interventions. The coexistence of several conditions creates a more complex disease status which

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3 271 requires additional considerations and care for the patient to experience the desired benefit from the
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5 272 provided interventions. The SOAD cohort will help us to identify these patients with complex needs,
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7 273 opening a venue for the development of better treatment approaches. Ultimately, the cohort has the
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9 274 potential to impact on the way OA is managed when other comorbidities coexist, potentially reducing the
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11 275 huge burden of this disease.
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16 379 **Author contribution**

17
18 380 All authors participated in the design of the study. All authors read, provided feedback and approved the
19 381 final protocol.

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21
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23
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25 384 Research Council and The Swedish Rheumatology Association.

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28 385 **Data sharing**

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31 386 All information regarding individual patients is subject to confidentiality in accordance with The Public
32 387 Access to Information and Secrecy Act (SFS 2009:400) chapter 25 article 1. Therefore, we will be unable
33 388 to share any data included in the SOAD cohort.

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36 389 **Conflict of interest**

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39 390 AWD is employed at the Swedish Knee Arthroplasty Register (SKAR). JV, AMS, SF, EN, OR are employed
40 391 by the Centre of Registers Västra Götaland, Sweden. AWD is employed at the Swedish Knee Arthroplasty
41 392 Register (SKAR). LED is the Co-founder and Chief Medical Officer of Joint Academy, a company which
42 393 provides web-based non-surgical interventions for patients with hip and knee osteoarthritis. AA is
43 394 employed by the Better management of OsteoArthritis register (BOA). All the other authors have nothing
44 395 to disclose

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51 397 **Word count: max 4,000**

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399 Table 1. Description of the single variables collected from the Better Management of Patients
400 with Osteoarthritis Register (BOA)

BOA Register		Baseline	Evaluation 3 months	Evaluation 12 months
Variable category	Variable			
Date	Date of visits	x	x	x
<i>Patient-reported measures</i>	Age, sex, weight, height	x		
	Smoking	x		
	Most affected joint (hip, knee or hand)	x	x	x
	Other affected joints	x	x	x
	Fear avoidance	x	x	x
	Request for surgery	x	x	x
	Walking difficulties	x	x	x
Physical activity level	Duration of physical training ^{a)}	x	x	x
	Duration of physical activity ^{b)}	x	x	x
Satisfaction	Satisfaction with treatment		x	x
Musculoskeletal comorbidity	Charnley class ^{c)}	x	x	x
Pain	Pain severity ^{d)} NRS	x	x	x
	Pain frequency	x	x	x
Generic	EQ-5D	x	x	x
Self-efficacy	Arthritis self-efficacy scale	x	x	x
<i>Physiotherapist-reported measures</i>	Earlier radiography/MRI/surgery in the most affected or the contralateral joint	x		
	Earlier treatments (including physiotherapy/adapted training/information on weight reduction/pharmaceuticals)	x		
	Waiting list for surgery	x	x	
	Use of medications for OA	x	x	
Follow-up	Radiography/MRI/surgery in the most affected or the contralateral joint since last evaluation		x	
	Compliance with intervention		x	

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3 401 a) Answering to the question: “During a regular week, how much time do you spend exercising on a level that
4 402 makes you short winded, for example running, fitness class, or ball games?” graded on categorical scale from “0”
5 403 to “more than 120 minutes”.
6 404 b) Answering to the question: “During a regular week, how much time are you physically active in ways that are not
7 405 exercise, for example walks, bicycling, or gardening?” graded on categorical scale from “0” to “more than 300
8 406 minutes”. [25]
9 407 NRS: Numeric Rating Scale, VAS: visual analogue scale, MRI: magnetic resonance imaging
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409 Table 2. Description of single variables collected from the Swedish Hip Arthroplasty Register

Swedish Hip Arthroplasty Register		Baseline	Follow-up 1, 6 and 10 year
Variable category	Variables		
<i>Surgery-related variables</i>			
Diagnosis (at hip)	ICD-10	x	
	Laterality	x	
Date	Date of surgery	x	
Type of surgery	Primary, revision, other reoperation	x	
Type of replacement	Total, partial, resurfacing hip replacement	x	
Patient status	Age, sex, height , weight, ASA class	x	
Implant characteristics	Article number, type of implant	x	
Technique	Incision, fixation	x	
<i>Patient-reported measures</i>			
Smoking status	Smoking (never, ex, daily, not daily))	x	
Musculoskeletal comorbidity	Charnley class ^{a)}	x	x
		x	x
Generic	EQ-5D	x	x
Treatment before hip replacement surgery	Physiotherapy	x	
	Standardised core treatment of education and supervised exercises	x	
Disease specific	Hip pain (Likert)	x	x
Satisfaction	Satisfaction with treatment (Likert)		x

410 ^{a)} Charnley class: classifications of musculoskeletal impairment. Class A corresponds to unilateral hip disease; Class
 411 B bilateral hip disease; and Class C indicates multiple joint disease or some other condition that inhibits the
 412 patient's ability to walk.

413 ICD-10, International Classification of Diseases, tenth revision; VAS, visual analogue scale. ASA-class, American
 414 Society of Anesthesiologists physical status classification system

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416 Table 3. Description of single variables collected from the Swedish Knee Arthroplasty Register

Swedish Knee Arthroplasty Register		Baseline	Follow-up 1 year
Variable category	Variable		
<i>Surgery-related variables</i>			
Diagnosis (at knee)	ICD-10	x	
	Laterality	x	
Date	Date of surgery	x	
Type of surgery	Primary, revision	x	
Type of replacement	Total, uni-compartmental, stabilised (hinged) knee replacement	x	
Patient status	Age, sex, height, weight, ASA class	x	
Implant characteristics	Article number, type of implant	x	
Technique	Incision, fixation	x	
<i>Patient-reported measures</i>			
Musculoskeletal comorbidity	Charnley class (modified) ^{a)}	x	x
		x	x
Generic	EQ-5D	x	x
Satisfaction	Satisfaction with treatment (VAS)		x
Disease specific	Knee injury and Osteoarthritis Outcome Score (KOOS), Knee pain (VAS)	x	x

417 ^{a)} Charnley class: classifications of musculoskeletal impairment. Class A: unilateral knee disease; Class B1: bilateral
 418 OA, one knee is scheduled for or already received arthroplasty surgery while the other knee has OA but no
 419 scheduled arthroplasty surgery; B2: bilateral OA, one knee is scheduled for or already received arthroplasty
 420 surgery while the other knee has already received knee arthroplasty surgery; Class C to multiple joint disease or
 421 some other condition that inhibits the patient's ability to walk.
 422 ICD-10, International Classification of Diseases, tenth revision; VAS, visual analogue scale. ASA-class, American
 423 Society of Anesthesiologists physical status classification system

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425 Table 4. Description of single variables collected from the National Diabetes Register

National diabetes register

Variable category	Variable
Patient's characteristics	Age (years), sex, height, weight, BMI
Diabetes characteristics	Type of diabetes, HbA1c(mmol/mol), debut year of diabetes, diabetes duration (years), age at onset
Diabetes treatment	Diet only, insulin, tablets, tablets and insulin
Method of insulin delivery	Insulin Pump Treatment (CSI), multiple daily injections (MDI)
Blood pressure	Systolic blood pressure (mmHg), Diastolic blood pressure (mmHg)
Cholesterol	Total cholesterol (mmol/L), LDL (mmol/L), HDL (mmol/L)
HbA1c	Triglycerides (mmol/L)
Renal function	Creatinine ($\mu\text{mol/L}$), eGFR (mL/min/1.73 m ²)
Retinopathy	Retinopathy (yes/no)
Other treatments	Anti-hypertensive treatment, Lipid-lowering treatment,
Physical Activity	Times per week of moderate to intense physical activity
Smoking status	Smoking (yes/no)
Albuminuria	Micro albuminuria, macro albuminuria (%)

426 Variables are measured at least once per year for patients with diabetes type 2 and four times per year for patients
 427 with diabetes type 1. If the patient has specific problems variables may be recorded with higher frequency.
 428 BMI: body mass index; HbA1: Haemoglobin subunit alpha 1; LDL: low density lipoprotein, HDL: high density
 429 lipoprotein; eGFR: estimated glomerular filtration rate

430 Table 5. Exposure and outcome for the study populations and examples of confounders and
 431 effect modifiers for the study analyses.

Population	Exposure	Outcome	Example confounders and effect modifiers
People with OA			
undergoing self-management treatment	diabetes	<ul style="list-style-type: none"> • Pain intensity • Pain frequency • Walking difficulties • Quality of life • Use of pain medications • Sick leave 	<ul style="list-style-type: none"> • Patient characteristics (age, sex, BMI, smoking) • Type of diabetes • Diabetes medications • Diabetes severity (for example HbA1c, blood pressure, cholesterol levels, albuminuria) • Disease progression (age at diagnosis, duration of disease) • Diabetes related complications (for example ocular bottom changes, kidney disease, neuropathy) • Cardiovascular comorbidities • Physical activity
Undergoing surgical OA treatment	diabetes	<ul style="list-style-type: none"> • Implant survival • Reoperation within 2 years • Change in patient reported outcome measures • Adverse events (for example cardiovascular events) • Mortality 	<ul style="list-style-type: none"> • Patient characteristics (age, sex, BMI, smoking) • Type of diabetes • Diabetes medications • Diabetes severity (for example HbA1c, blood pressure, cholesterol levels, albuminuria) • Disease progression (age at diagnosis, duration of disease) • Diabetes related complications (for example ocular bottom changes, kidney disease, neuropathy) • Cardiovascular comorbidities
Diabetes			
	non-surgical OA treatment of hip and knee	<ul style="list-style-type: none"> • Diabetes Medications (diabetes, blood sugar, lipid and blood pressure lowering) • Diabetes severity (for example HbA1, blood pressure, cholesterol levels, albuminuria) • Diabetes related complications (for example ocular bottom changes, kidney disease, neuropathy) 	<ul style="list-style-type: none"> • Patient characteristics (age, sex, BMI, smoking) • OA severity (pain intensity, pain frequency, walking difficulties, quality of life, pain medications, sick leave) • Cardiovascular comorbidities • Physical activity
	surgical OA treatment of hip and knee	<ul style="list-style-type: none"> • Diabetes Medications (diabetes, blood sugar, lipid and blood pressure lowering) • Diabetes severity (for example HbA1c, blood pressure, cholesterol levels, albuminuria) • Diabetes related complications (for example ocular bottom changes, kidney disease, neuropathy) 	<ul style="list-style-type: none"> • Patient characteristics (Age, Sex, Charnley classification, BMI) • Surgical technique • Implant characteristics • Cardiovascular comorbidities

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BMI: body mass index; OA: osteoarthritis; THR: total hip replacement; TKR: total knee replacement; HbA1: haemoglobin subunit alpha 1

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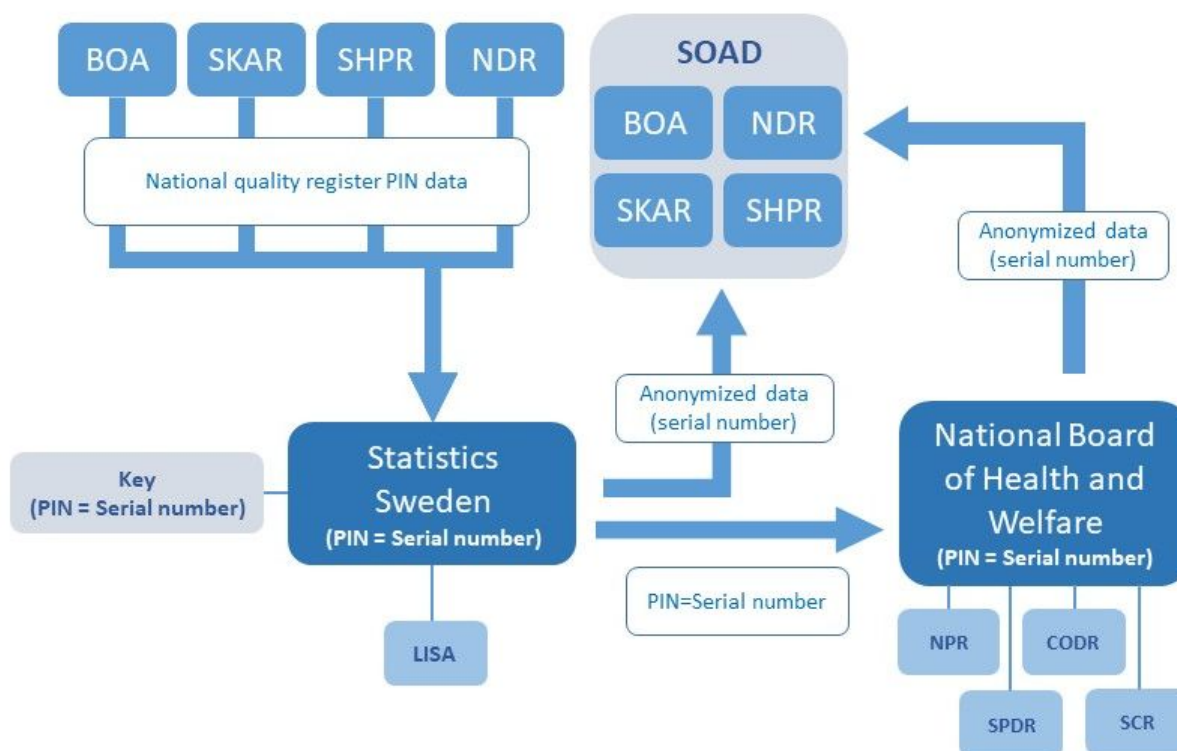


Figure 1. The data linkage process. Data from the four national quality registers Better Management of Patients with Osteoarthritis Register (BOA), Swedish Hip Arthroplasty Register (SHAR), Swedish Knee Arthroplasty Register (SKAR) and National Diabetes Register (NDR) is safely transferred to Statistics Sweden. Statistics Sweden will anonymise the data by replacing PIN with serial numbers. Data will be extracted from LISA (Longitudinal integration database for health insurance and labour market studies) and transferred to the entity principally responsible for the Swedish Osteoarthritis and Diabetes (SOAD) cohort research. The PIN and serial numbers will also be shared with National Board of Health and Welfare who will return data from National Patient Register (NPR), Swedish Prescribed Drug Register (SPDR), Cause of Death Register (CODR) and Swedish Cancer Register (SCR) to the entity principally responsible for the research. The linkage key will be saved at Statistics Sweden for 3 years to allow the possibility of adding more year cohorts or new variables to the research database if new research questions arise (with new ethical approval).

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1-2	
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5	
Objectives	3	State specific objectives, including any prespecified hypotheses	5	
Methods				
Study design	4	Present key elements of study design early in the paper	6-8	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8	
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-8	
		<i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls		
		<i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants		
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed		
		<i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9, table 5	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Table 1 to 4	
Bias	9	Describe any efforts to address potential sources of bias	9	
Study size	10	Explain how the study size was arrived at	Figure 1	

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9
		(b) Describe any methods used to examine subgroups and interactions	9
		(c) Explain how missing data were addressed	9
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	9
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N/A
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	N/A
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	N/A
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	N/A
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(b) Report category boundaries when continuous variables were categorized	N/A
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	N/A
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	N/A
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	N/A
Generalisability	21	Discuss the generalisability (external validity) of the study results	N/A
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Understanding the role of diabetes in the osteoarthritis disease and treatment process: a study protocol for The Swedish Osteoarthritis and Diabetes (SOAD) cohort

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-032923.R1
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Date Submitted by the Author:	06-Nov-2019
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Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Epidemiology, Rehabilitation medicine
Keywords:	osteoarthritis, General diabetes < DIABETES & ENDOCRINOLOGY, register, cohort, exercise, SURGERY

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4 **1 Understanding the role of diabetes in the osteoarthritis disease and treatment**
5 **2 process: a study protocol for The Swedish Osteoarthritis and Diabetes (SOAD)**
6 **3 cohort**

8
9 4 Dell'Isola A^{1*}, Vinblad J^{*2,3}, Lohmander LS¹, Svensson AM^{5,6}, Turkiewicz A⁴, Franzén S^{5,7}, Naclér E², W-
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53 27 Keywords: Osteoarthritis, diabetes, register, cohort, exercise, surgery.

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55 28 Word count: 3255

1
2
3 29 **ABSTRACT** (280 words)
4

5 30 **Introduction**
6

7
8 31 Osteoarthritis (OA) is the most common form of arthritis and a leading cause of disability worldwide.
9
10 32 Metabolic comorbidities such as type 2 diabetes occur with a higher rate in people with OA than in the
11
12 33 general population. Several factors including obesity, hyperglycemia toxicity and physical inactivity have
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14 34 been suggested as potential links between diabetes and OA, and have been shown to negatively impact
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16 35 patients' health and quality of life. However, little is known on the role of diabetes in determining the
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18 36 outcome of non-surgical and surgical management of OA, and at the same time, how different OA
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20 37 interventions may affect diabetes control. Thus, the overall aim of this project is to explore (1) the impact
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22 38 of diabetes on the outcome of non-surgical and surgical OA treatments, and (2) the impact of non-surgical
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24 39 and surgical OA treatments on diabetes control.

25
26 40 **Methods and analysis**
27

28 41 The study cohort is based on prospectively ascertained register data on a national level in Sweden. Data
29
30 42 from OA patients who received a first-line non-surgical intervention and are registered in the National
31
32 43 Quality Register for Better Management of Patients with Osteoarthritis will be merged with data from the
33
34 44 Swedish Knee and Hip Arthroplasty Registers and the National Diabetes Register. Additional variables
35
36 45 regarding patients' use of prescribed drugs, comorbidities, socioeconomic status, and cause of death will
37
38 46 be obtained through other national health and population data registers. The linkage will be performed
39
40 47 on an individual level using unique personal identity numbers.

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42 48 **Ethics and dissemination**
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44 49 This study received ethical approval (2019-02570) from the Swedish Ethical Review Authority. Results
45
46 50 from this cohort will be submitted to peer-reviewed scientific journals and reported at the leading national
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48 51 and international meetings in the field.
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3 53 **ARTICLE SUMMARY**
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5 54 **Strengths and limitations of this study**
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- 7
- 8 55 • This study will use a large nationwide population-based cohort based on data from national
9 56 quality registers with high coverage and completeness to explore the relationship between
10 57 diabetes and osteoarthritis (OA) and their related care process.
 - 11 58 • We will include data regarding both non-surgical and surgical treatments for patients with OA
12 59 giving the possibility to capture the influence of diabetes across the whole spectrum of OA
13 60 treatments.
 - 14 61 • We will include covariate information from several national registers that will allow to account
15 62 for potential confounders and effect modifiers.
 - 16 63 • A limitation of register-based studies is that the variables available and the characteristics of the
17 64 treatments provided are predetermined, i.e., it is not possible to add covariates, exposures or
18 65 outcomes (not in the registers) or to modify the interventions that have been given.
 - 19 66 • People included in the National Quality Register for Better Management of Patients with
20 67 Osteoarthritis (BOA) Register, the Swedish Hip Arthroplasty Register (SHAR), the Swedish Knee
21 68 Arthroplasty Register (SKAR) received an intervention due to OA. Due to the complexity of the OA
22 69 disease, treatments are individualised based on patient's and disease characteristics, which
23 70 implies that selection bias and confounding by indication may bias our estimates.
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72 INTRODUCTION

73 Osteoarthritis (OA) is the most common form of arthritis and affect mainly the knee and the hip joint [1].
74 In Sweden, more than 25% of the population aged >45 years is estimated to suffer from OA related pain
75 symptoms and associated physical activity restrictions [2]. The average annual cost for a person affected
76 by OA is reported to exceed €2,000, while the total European expense directly attributable to OA is
77 estimated to be as high as €700 billion [3].

78 In addition to the already huge health and societal burden of OA, recent studies suggest that OA patients
79 are twice as likely to have comorbidities compared to controls of the same age, indicating that the co-
80 occurrence of multiple conditions in OA patients is the norm rather than the exception [4]. For instance,
81 based on data showing a higher incidence of knee OA in overweight patients with metabolic disorders, a
82 metabolic OA phenotype has been hypothesised [5-7]. Among the metabolic disorders, diabetes seems
83 to play a central role due to its high prevalence and the toxic effect that hyperglycaemia has on the
84 cartilage and its cells, and to the motor and sensory system through peripheral neuropathy [8-10].

85 According to data from the Swedish National Diabetes Register (NDR), approximately 5% of the Swedish
86 population has diabetes, with type 2 diabetes accounting for approximately 90% of the cases [11]. Persons
87 with diabetes have a higher risk of developing cardiovascular diseases and have a 2- to 5-fold increased
88 risk of mortality compared with the general population [12].

89 In OA patients the prevalence of diabetes has been reported to be nearly three times higher than in the
90 general population [7]. Obesity is a shared risk factor for OA of the knee and the hip and diabetes and can
91 partially explain the association between these diseases [13, 14]. In addition to the mechanical overload
92 caused by the excess weight, adipocytes release cytokines into the bloodstream promoting chronic low-
93 grade inflammation and activating proteolytic enzymes which can trigger matrix degradation and initiate
94 OA. At the same time, adipose-induced low-grade inflammation influences the metabolic dysregulation
95 underlying several metabolic disorders among others, diabetes type II [14].

96 Once diabetes is initiated, it further promotes cartilage degeneration and joint inflammation causing
97 enrichment of advanced glycation endproducts (AGEs) and matrix stiffening preventing optimal
98 cushioning of the joint [7, 15]. This process leads to a worsening in OA symptoms promoting physical
99 inactivity and weight gain and creating a vicious cycle which maintains the metabolic dysregulation and
100 increases joint symptoms [13, 16-18].

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3 101 The evidence-based first-line management for people with hip and knee OA includes education and
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5 102 exercise, which are recommended regardless of OA disease severity, and weight loss for those overweight
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7 103 [19]. Metabolic comorbidities may have a significant impact on the treatment, partially explaining the lack
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9 104 of response experienced by some patients.

10
11 105 Replacement of the knee and of the hip is an effective treatment for patients with severe OA who do not
12
13 106 sufficiently improve after non-surgical management [20]. Due to the rising prevalence of OA and the
14
15 107 growing demand for this procedure, the number of hip and knee replacements has dramatically increased.
16
17 108 In Sweden (total population 10 million), 14,700 primary total hip replacements (THRs) and nearly 14,000
18
19 109 total knee replacements (TKRs) were performed in 2017 with OA as indication. These figures account for
20
21 110 81% and 97% of the annual hip and knee replacements respectively, and translates in an annual incidence
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23 111 of nearly 150 procedures per 100,000 persons for both THR and TKR [21, 22].

24
25 112 Considering the association between diabetes and OA, surprisingly little is known regarding the influence
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27 113 that diabetes has on the outcome of OA treatments (both non-surgical and surgical) [23, 24]. In addition,
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29 114 no evidence exists regarding the effect that OA treatments (both non-surgical and surgical) may have on
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31 115 diabetes control (both for type I and type II). Thus, merging data from multiple Swedish registers will allow
32
33 116 us to follow patients with knee and hip OA through the progress of their disease to understand how
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35 117 diabetes influences the OA disease process. This study cohort is created to increase knowledge of the
36
37 118 influence that diabetes has on the outcomes of OA patients who have received non-surgical and/or
38
39 119 surgical treatments for hip and knee OA, and the influence that hip and knee OA and its treatments have
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41 120 on the diabetes control.

42 121 **METHODS AND ANALYSIS**

43 122 **Research questions**

44
45 123 In order to understand how the coexistence of OA of the hip or of the knee and diabetes influences the
46
47 124 treatment effects in these diseases, a series of research questions have been posed. The research
48
49 125 questions cover two main thematic areas: (1) the impact of diabetes on the outcome of non-surgical and
50
51 126 surgical OA treatments, and (2) the impact of OA non-surgical and surgical OA treatments on diabetes
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53 127 control (consideration to type of diabetes (I or II) will be taken).

54 128 Area 1

- 55 129 1. What is the prevalence of diabetes in people with OA undergoing a non-surgical intervention?

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3 130 2. Is the presence of diabetes, diabetes-related factors (e.g. type of diabetes, diabetes-related
4 medication, blood pressure, HbA1c) associated with OA severity (e.g. pain intensity, pain
5 131 frequency, walking difficulties) of people with OA undergoing a self-management non-surgical
6 132 intervention?
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9
10 134 3. Is the presence of diabetes and diabetes-related factors associated with the outcomes of a self-
11 135 management non-surgical intervention for people with OA (e.g. change in pain levels, pain
12 frequency, walking difficulties)?
13 136
14
15 137 4. Is the presence of diabetes and diabetes-related factors associated with the risk of joint
16 138 replacement in people with OA who underwent a self-management non-surgical intervention?
17
18 139 5. What is the incidence of reoperations and other adverse events such as thromboembolism,
19 cardiovascular events and mortality following primary total hip or knee replacement due to OA in
20 140 people with or without diabetes?
21 141
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23 142 6. What diabetes-related factors are associated with the risk of reoperation and other adverse
24 events following primary total hip or knee replacement among person with diabetes?
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27 144 Area 2
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30 145 7. How does a self-management non-surgical intervention for OA influence diabetes (type I vs type
31 146 II) control (e.g. change in diabetes drug intake after the intervention, change in Hb A1c levels after
32 the intervention) compared to comparable people with diabetes who had not taken part in the
33 147 intervention?
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36 149 8. How does primary total hip or knee replacement influence the diabetes control compared to
37 comparable persons with diabetes but with no history of hip or knee arthroplasty?
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40 151 9. What diabetes-related risk factors are associated with diabetes control following primary total
41 hip or knee replacement due to OA?
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153 **Main exposures and outcomes**

154 The exposure and outcome measures are described in table 1. Potential confounding factors for main
155 analysis and disease sub analysis are described with examples.

156 INSERT TABLE 1 HERE

157 **The Swedish OA and Diabetes cohort (SOAD)**

158 This nationwide observational study cohort (SOAD) will be based on prospectively obtained individual-
159 level data from four main sources: the National Quality Register for Better Management of Patients with
160 Osteoarthritis (BOA) Register, the Swedish Hip Arthroplasty Register (SHAR), the Swedish Knee
161 Arthroplasty Register (SKAR), and the Swedish National Diabetes Register (NDR). Data starting from the
162 year of each register establishment will be merged using the unique personal identity number (PIN) issued
163 to all legal residents in Sweden. Additional variables regarding patients' use of prescribed drugs,
164 comorbidities, cause of death, and socioeconomic information will be obtained through the following
165 population-based registers:

- 166 • The Swedish Prescribed Drug Register (SPDR) held by the National Board of Health and Welfare.
- 167 • The National Patient Register (NPR) held by the National Board of Health and Welfare; information
168 regarding in-hospital diagnoses and outpatient specialist care diagnoses, e.g. interventions,
169 adverse events such as thromboembolism or other comorbid conditions.
- 170 • Swedish Cancer Register, The National Board of Health and Welfare.
- 171 • The Cause of death Register (CODR) held by the National Board of Health and Welfare
- 172 • Longitudinal integration database for health insurance and labour market studies (LISA) held by
173 Statistics Sweden for data such as marital status, educational level and country of origin.

174 **Data sources**

175 BOA: The BOA register was started in 2008 and currently includes more than 100,000 individuals with OA
176 who have registered for an evidence-based self-management programme. These patients sought
177 treatment for knee and/or hip pain in primary healthcare in Sweden and were referred for standardised
178 core treatment (education and supervised exercises) after a confirmed clinical/radiographic OA diagnosis
179 in accordance with the recommendations for OA diagnosis from the Swedish National Board of Health
180 and Welfare [25]. These guidelines are in line with internationally accepted diagnostic criteria, and
181 according to the guidelines, radiographic examination should only be used in uncertain cases, if the

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3 182 patient is not responding to treatment or when a surgical intervention is planned [26, 27]. BOA offers all
4
5 183 the patients two education sessions focusing on the pathophysiology of OA and the benefit of exercise
6
7 184 which are mandatory for participating in the second (exercise) of the programme. A third, optional,
8
9 185 session held by a trained osteoarthritis communicator (a patient with osteoarthritis who previously
10
11 186 participated in BOA) is offered to provide a patient's perspective on OA self-management and to teach
12
13 187 about the lived experience with this condition, as well as his or her personal experience of non-surgical
14
15 188 interventions. After the education, participants can take part in the exercise phase of BOA which consists
16
17 189 of a face-to-face session with a physiotherapist. In this session, the patients receive a personalised
18
19 190 intervention programme and the necessary instructions to perform it independently at home. Thereafter,
20
21 191 participants are given the possibility to perform their exercise programme on their own or to participate
22
23 192 in up to 12 supervised group exercise session with a physiotherapist provided two times a week for six
24
25 193 weeks. Thus, the register contains two separate cohorts that performed, in addition to the education
26
27 194 sessions, either home exercise or supervised exercise. The register has a data completeness of almost 90%
28
29 195 and the BOA participants have answered validated and patient-relevant socio-demographic and outcome
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31 196 questionnaires at baseline, after the interventions (two to five months) and at one year (12-15 months)
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33 197 (Table 2).

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31 198 INSERT TABLE 2 HERE

34 199 SHAR: Started in 1979, SHAR registers primary hip replacement operations and reoperations in Sweden
35
36 200 including individual patient data, surgical technique and type of implant used. Since 2002 patient-reported
37
38 201 measures such as joint pain, HRQoL and satisfaction with treatment have also been collected before
39
40 202 surgery and one, six and ten years postoperatively. The register encompasses 318 000 primary total hip
41
42 203 replacements due to OA and 61 500 reoperations after total hip replacements where OA was the main
43
44 204 reason for the primary surgery (at the end of 2018). The register has overall data completeness of 98,5%
45
46 205 (2016) including all indications for total hip replacements (Table 3).

46 206 SKAR: The Swedish Knee Arthroplasty Register is a Swedish National Quality Register founded in 1975.
47
48 207 The register collects individual patient data, surgical technique and type of implant used for patients who
49
50 208 undergo knee replacement. The SKAR also collects information on re-operations/revision surgery. SKAR
51
52 209 has completeness of 98.1 % (2016) and have registered almost 270,000 primary knee replacements due
53
54 210 to OA and more than 21 400 revisions at the end of 2018 (Table 4).

55 211 INSERT TABLE 3 AND 4 HERE

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3 212 NDR: NDR has been a Swedish National Quality Register since 1996 and collects data on clinical
4 213 characteristics, risk factors, laboratory analyses, complications of diabetes, and medications for patients
5 214 18 years of age or older with a diagnosis of diabetes (Table 5). The completeness is 96.5 % (2017) and the
6 215 register has 750 004 (2017) unique individuals in their database. More than 95% of all individuals with
7 216 type 1 diabetes mellitus (T1DM) and 90% of individuals with type 2 diabetes mellitus (T2DM) in Sweden
8 217 are included in the NDR.

13
14 218 INSERT TABLE 5 HERE

16 219 **Data linkage**

18 220 Personal Identity Number (PIN): In Sweden, all legal residents are registered with a unique PIN that
19 221 provides information on the date of birth and sex. Swedish law requires all documentation regarding
20 222 healthcare contacts to be registered using the patient's PIN [28]. The PIN is also used for registration of
21 223 data for statistics such as national population-based registers and healthcare quality registers [29, 30].
22 224 The system allows for linkage of data at an individual level between the different registers in Sweden with
23 225 the possibility of creating merged research databases for epidemiological research on large populations,
24 226 after the relevant ethical approval has been obtained. Data linkage for the current study will include all
25 227 the data available in BOA, SHPR, SKAR and NDR and it will start from the first time point available in the
26 228 registers. The data linkage process has been initiated and it is described in figure 1. Data linkage is
27 229 expected to be completed by 2020. Estimated start and end dates for the project are 01/09/2020 and
28 230 01/09/2030 respectively.

36
37 231 INSERT HERE FIGURE 1

40 232 **Analysis plan**

42 233 Data harmonisation will be performed, the more reliable data source will be used to guarantee
43 234 information quality and reliability across exposed and unexposed subjects. To establish the reliability of
44 235 the source we will consider how the measurement was performed (e.g self-reported vs measured) and
45 236 data quality (e.g. percentage of missing). If the same variable (e.g. BMI) will be present in the source
46 237 deemed as most reliable at more than one time-point, we will use the measurement closest to the time
47 238 point of interest.

52
53 239 We will develop a specific statistical analysis plan for each specific study that will be conducted within
54 240 SOAD. These will follow several general principles. We will aim for the inclusion of all available knee and

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3 241 hip OA and diabetes patients to limit potential selection bias. We will use multiple imputation methods to
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5 242 impute the missing data on exposures, outcomes and confounders, when relevant. The imputation model
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7 243 will be specific for each study and compatible with the chosen analysis model. For example, the fully
8
9 244 conditional specification (also called chained equations) may be used to enable flexible models for proper
10
11 245 imputation of all variables. In the statistical modelling we will aim for estimation of causal effects and
12
13 246 statistical models will be chosen accordingly using direct acyclic graphs (DAGs) to enable proper
14
15 247 confounding control [31]. For confounding control, we will use regression models or inverse probability
16
17 248 weighting. For analysis of panel data (i.e. longitudinal repeated measurements of the participants and/or
18
19 249 data clustered by caregiver) we will use multilevel regression models. For time-to-event data we will use
20
21 250 the proportional hazards Cox regression model, or, if appropriate, parametric models. For mediation
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23 251 analysis, we will use linear models or maximum likelihood structural equation models when appropriate.
24
25 252 For categorical outcomes we will use other approaches [32, 33]. We will report the results from all
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27 253 analyses as relevant estimated effect size (such as risk differences, risk ratios or hazard ratios) with 95%
28
29 254 confidence intervals and interpret these for clinical relevance, irrespectively of statistical significance [34,
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31 255 35].

32
33 256 For the current study, we did not perform any power calculation. This because the question of power can
34
35 257 be considered secondary in such a setting where the sample size is driven by data availability and not
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37 258 decided a priori. In addition, when interpreting results, we will not use the concept of statistical
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39 259 significance, but we will base our interpretation on effect sizes (and the uncertainty around them) and
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41 260 clinical relevance [36]. Therefore, we will include all the available data, with ~100,000 BOA participants,
42
43 261 whereof an estimated 15,000 have diabetes [37]. Regarding the SHAR and SKAR, we will have data for 240
44
45 262 000 and 320 000 joint replacements respectively. Based on previous studies we expect that the prevalence
46
47 263 of diabetes will be around 8% and 14% among patients undergoing THR and TKR, respectively [38, 39].
48
49 264 We expect that this will enable precise estimations of the main effects of interest.

265 **Patient and public involvement**

266 Patient representatives were not involved in the development of the research question or the design of
267 this study. However, patients were involved in the creation of the BOA supported self-management
268 programme and contributed to the development of the key contents of the programme [40]. Patients are
269 also actively involved in the BOA programme and deliver a compulsory education session where the
270 patient's perspective on OA self-management treatment is explored. The Swedish Hip and Knee
271 Arthroplasty Registers have patient representatives on their respective steering committees.

272 ETHICS AND DISSEMINATION

273 Storage and management of data

274 Ethical approval for the creation of the cohort and the analyses as detailed in the present protocol has
275 been obtained (14th May 2019, 2019-02570). A copy of the full data set will be stored at the Center of
276 Registers Västra Götaland, Gothenburg, Sweden. A second copy of the full data set will be stored at Lund
277 University on the platform LUSEC (Lund information security platform). The platforms are designed to
278 securely store, manage and analyse data in accordance with the European Union general data protection
279 regulation (GDPR). The process of linkage, storage and management of data, the role of informed consent
280 in register-based research and safeguarding the integrity of study participants follows the legal and ethical
281 frameworks as described by Swedish law and ethical boards. This has been described by Ludvigsson et al
282 [28].

283 Dissemination

284 The results from this study will be published in peer-reviewed scientific journals and will be presented at
285 the leading national and international meetings in the field. The results will also be disseminated through
286 annual reports published on the registers' websites in order to reach clinicians working with people with
287 OA and diabetes.

288 In order to reach people suffering from OA and diabetes, we aim to exploit the connection between BOA
289 people seeking care for OA. Briefly, we will target BOA educators providing them material (through email
290 and mail) regarding the progress and achievement of the project focusing on the impact that the
291 coexistence of OA and diabetes has on the treatment. In this way, we will reach the new patients taking
292 part in BOA that will be better informed about their condition and about the strategy to undertake in
293 order to maximise the benefit of first-line intervention.

294 Finally, In SOAD we recognize the importance of reaching a broad audience, for this reason, we will utilise
295 the authors Twitter and Facebook networks to create awareness among the general public of the
296 importance of the issue. The social media will help us to make scientific practice easily accessible and
297 understandable to an audience of non-specialists.

298

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3 299 **DISCUSSION**
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5
6 300 This study cohort will provide unique insights into the relationships between diabetes and OA. By using
7 301 data from the BOA, SHAR, SKAR and NDR registers we will be able to investigate the influence of diabetes
8
9 302 on the outcome of non-surgical and surgical OA interventions as well as the effect of OA treatments on
10
11 303 diabetes control.

12
13 304 To our knowledge, this will be the largest dataset combining data on OA and diabetes management.
14
15 305 Thanks to the large sample size on a national level, results arising from this study will likely have high
16
17 306 external validity and generalisability. However, treatment data collected in national registers are likely to
18
19 307 be influenced by the regional differences in treatment protocols and data collection that characterise
20
21 308 different clinical environments when compared to e.g. highly standardised clinical trials.

22
23 309 In conclusion, to optimise treatments for OA and diabetes and move towards a personalised-care
24
25 310 approach, it is important to identify factors and comorbidities that may negatively influence the outcome
26
27 311 of the interventions. The coexistence of several conditions creates a more complex disease status which
28
29 312 requires additional considerations and cares for the patient to experience the desired benefit from the
30
31 313 provided interventions. The SOAD cohort will help us to identify these patients with complex needs,
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33 314 opening a venue for the development of better treatment approaches. Ultimately, the cohort has the
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35 315 potential to impact on the way OA is managed when other comorbidities coexist, potentially reducing the
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37 316 huge burden of this disease.
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422 **Author contribution**

423 DA, VJ, LLS, SAM, TA, FS, NE, WA, AA, DL, RO, EM provided substantial contributions to the conception,
424 design of the work and analysis plan of data. DA, VJ, LLS, SAM, TA, FS, NE, WA, AA, DL, RO, EM contributed
425 to the drafting of the protocol and approved the final version.

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428 Research Council and The Swedish Rheumatology Association.

429 **Data sharing**

430 All information regarding individual patients is subject to confidentiality in accordance with The Public
431 Access to Information and Secrecy Act (SFS 2009:400) chapter 25 article 1. Therefore, we will be unable
432 to share any data included in the SOAD cohort.

433 **Conflict of interest**

434 AWD is employed at the Swedish Knee Arthroplasty Register (SKAR). JV, AMS, SF, EN, OR are employed by
435 the Centre of Registers Västra Götaland, Sweden. AWD is employed at the Swedish Knee Arthroplasty
436 Register (SKAR). LD is the Co-founder and Chief Medical Officer of Joint Academy, a company which
437 provides web-based non-surgical interventions for patients with hip and knee osteoarthritis. AA is employed
438 by the Better management of OsteoArthritis register (BOA). All the other authors have nothing to disclose

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440 Table 1. Exposure and outcome for the study populations and examples of confounders and
 441 effect modifiers for the study analyses.

Population	Exposure	Outcome	Example confounders and effect modifiers
People with OA			
undergoing self-management treatment	diabetes	<ul style="list-style-type: none"> • Pain intensity • Pain frequency • Walking difficulties • Quality of life • Use of pain medications • Sick leave 	<ul style="list-style-type: none"> • Patient characteristics (age, sex, BMI, smoking) • Type of diabetes • Diabetes medications • Diabetes severity (for example HbA1c, blood pressure, cholesterol levels, albuminuria) • Diabetes disease duration (age at diagnosis, duration of disease) • Diabetes related complications (for example ocular bottom changes, kidney disease, neuropathy) • Cardiovascular comorbidities • Physical activity • Weight Change
Undergoing surgical OA treatment	diabetes	<ul style="list-style-type: none"> • Implant survival • Reoperation within 2 years • Change in patient reported outcome measures • Adverse events (for example cardiovascular events) • Mortality 	<ul style="list-style-type: none"> • Patient characteristics (age, sex, BMI, smoking) • Type of diabetes • Diabetes medications • Diabetes severity (for example HbA1c, blood pressure, cholesterol levels, albuminuria) • Disease progression (age at diagnosis, duration of disease) • Diabetes related complications (for example ocular bottom changes, kidney disease, neuropathy) • Cardiovascular comorbidities • Weight Change
Diabetes			
	non-surgical OA treatment of hip and knee	<ul style="list-style-type: none"> • Diabetes Medications (diabetes, blood sugar, lipid and blood pressure lowering) • Diabetes severity (for example HbA1, blood pressure, cholesterol levels, albuminuria) • Diabetes related complications (for example ocular bottom changes, kidney disease, neuropathy) 	<ul style="list-style-type: none"> • Patient characteristics (age, sex, BMI, smoking) • OA severity (pain intensity, pain frequency, walking difficulties, quality of life, pain medications, sick leave) • Type of diabetes • Cardiovascular comorbidities • Physical activity • Weight Change
	surgical OA treatment of hip and knee	<ul style="list-style-type: none"> • Diabetes Medications (diabetes, blood sugar, lipid and blood pressure lowering) • Diabetes severity (for example HbA1c, blood pressure, cholesterol levels, albuminuria) • Diabetes related complications (for example 	<ul style="list-style-type: none"> • Patient characteristics (Age, Sex, Charnley classification, BMI) • Type of diabetes • Surgical technique • Implant characteristics • Cardiovascular comorbidities • Weight Change

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ocular bottom changes,
kidney disease, neuropathy)

BMI: body mass index; OA: osteoarthritis; THR: total hip replacement; TKR: total knee replacement; HbA1: haemoglobin subunit alpha 1

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For peer review only

443 Table 2. Description of the single variables collected from the Better Management of Patients
 444 with Osteoarthritis Register (BOA)

BOA Register		Baseline	Evaluation 3 months	Evaluation 12 months
Variable category	Variable			
Date	Date of visits	x	x	x
<i>Patient-reported measures</i>	Age, sex, weight, height	x		
	Smoking	x		
	Most affected joint (hip, knee or hand)	x	x	x
	Other affected joints	x	x	x
	Fear avoidance	x	x	x
	Request for surgery	x	x	x
	Walking difficulties	x	x	x
Physical activity level	Duration of physical training ^{a)}	x	x	x
	Duration of physical activity ^{b)}	x	x	x
Satisfaction	Satisfaction with treatment		x	x
Musculoskeletal comorbidity	Charnley class ^{c)}	x	x	x
Pain	Pain severity ^{d)} NRS	x	x	x
	Pain frequency	x	x	x
Generic	EQ-5D	x	x	x
Self-efficacy	Arthritis self-efficacy scale	x	x	x
<i>Physiotherapist-reported measures</i>	Earlier radiography/MRI/surgery in the most affected or the contralateral joint	x		
	Earlier treatments (including physiotherapy/adapted training/information on weight reduction/pharmaceuticals)	x		
	Waiting list for surgery	x	x	
	Use of medications for OA	x	x	
Follow-up	Radiography/MRI/surgery in the most affected or the contralateral joint since last evaluation		x	
	Compliance with intervention		x	

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3 445 a) Answering to the question: "During a regular week, how much time do you spend exercising on a level that
4 446 makes you short winded, for example running, fitness class, or ball games?" graded on categorical scale from "0"
5 447 to "more than 120 minutes".
6 448 b) Answering to the question: "During a regular week, how much time are you physically active in ways that are not
7 449 exercise, for example walks, bicycling, or gardening?" graded on categorical scale from "0" to "more than 300
8 450 minutes".[25]
9 451 c) Charnley class: classifications of musculoskeletal impairment. Class A corresponds with unilateral hip or knee OA;
10 452 class B bilateral hip or knee OA and class C indicates multiple joint OA or some other condition that inhibits the
11 453 patient's ability to walk
12 454 d) Answering to: "Select the box that corresponds to your average pain from your most affected joint the last
13 455 week".
14 456 NRS: Numeric Rating Scale, VAS: visual analogue scale, MRI: magnetic resonance imaging
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458 Table 3. Description of single variables collected from the Swedish Hip Arthroplasty Register

Swedish Hip Arthroplasty Register		Baseline	Follow-up 1, 6 and 10 year
Variable category	Variables		
<i>Surgery-related variables</i>			
Diagnosis (at hip)	ICD-10	x	
	Laterality	x	
Date	Date of surgery	x	
Type of surgery	Primary, revision, other reoperation	x	
Type of replacement	Total, partial, resurfacing hip replacement	x	
Patient status	Age, sex, height , weight, ASA class	x	
Implant characteristics	Article number, type of implant	x	
Technique	Incision, fixation	x	
<i>Patient-reported measures</i>			
Smoking status	Smoking (never, ex, daily, not daily))	x	
Musculoskeletal comorbidity	Charnley class ^{a)}	x	x
		x	x
Generic	EQ-5D	x	x
Treatment before hip replacement surgery	Physiotherapy	x	
	Standardised core treatment of education and supervised exercises	x	
Disease specific	Hip pain (Likert)	x	x
Satisfaction	Satisfaction with treatment (Likert)		x

459 ^{a)} Charnley class: classifications of musculoskeletal impairment. Class A corresponds to unilateral hip disease; Class
 460 B bilateral hip disease; and Class C indicates multiple joint disease or some other condition that inhibits the
 461 patient's ability to walk.

462 ICD-10, International Classification of Diseases, tenth revision; VAS, visual analogue scale. ASA-class, American
 463 Society of Anesthesiologists physical status classification system

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465 Table 4. Description of single variables collected from the Swedish Knee Arthroplasty Register

Swedish Knee Arthroplasty Register		Baseline	Follow-up 1 year
Variable category	Variable		
<i>Surgery-related variables</i>			
Diagnosis (at knee)	ICD-10	x	
	Laterality	x	
Date	Date of surgery	x	
Type of surgery	Primary, revision	x	
Type of replacement	Total, uni-compartmental, stabilised (hinged) knee replacement	x	
Patient status	Age, sex, height, weight, ASA class	x	
Implant characteristics	Article number, type of implant	x	
Technique	Incision, fixation	x	
<i>Patient-reported measures</i>			
Musculoskeletal comorbidity	Charnley class (modified) ^{a)}	x	x
		x	x
Generic	EQ-5D	x	x
Satisfaction	Satisfaction with treatment (VAS)		x
Disease specific	Knee injury and Osteoarthritis Outcome Score (KOOS), Knee pain (VAS)	x	x

466 ^{a)} Charnley class: classifications of musculoskeletal impairment. Class A: unilateral knee disease; Class B1: bilateral
467 OA, one knee is scheduled for or already received arthroplasty surgery while the other knee has OA but no
468 scheduled arthroplasty surgery; B2: bilateral OA, one knee is scheduled for or already received arthroplasty
469 surgery while the other knee has already received knee arthroplasty surgery; Class C to multiple joint disease or
470 some other condition that inhibits the patient's ability to walk.
471 ICD-10, International Classification of Diseases, tenth revision; VAS, visual analogue scale. ASA-class, American
472 Society of Anesthesiologists physical status classification system

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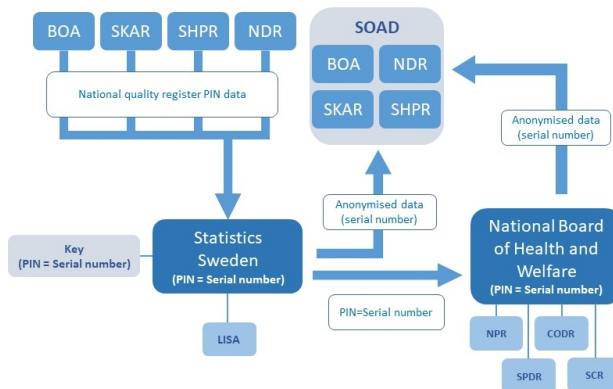
474 Table 5. Description of single variables collected from the National Diabetes Register

National diabetes register

Variable category	Variable
Patient's characteristics	Age (years), sex, height, weight, BMI
Diabetes characteristics	Type of diabetes, HbA1c(mmol/mol), debut year of diabetes, diabetes duration (years), age at onset
Diabetes treatment	Diet only, insulin, tablets, tablets and insulin
Method of insulin delivery	Insulin Pump Treatment (CSI), multiple daily injections (MDI)
Blood pressure	Systolic blood pressure (mmHg), Diastolic blood pressure (mmHg)
Cholesterol	Total cholesterol (mmol/L), LDL (mmol/L), HDL (mmol/L)
HbA1c	Triglycerides (mmol/L)
Renal function	Creatinine ($\mu\text{mol/L}$), eGFR (mL/min/1.73 m ²)
Retinopathy	Retinopathy (yes/no)
Other treatments	Anti-hypertensive treatment, Lipid-lowering treatment,
Physical Activity	Times per week of moderate to intense physical activity
Smoking status	Smoking (yes/no)
Albuminuria	Micro albuminurea, macro albuminurea (%)

475 Variables are measured at least once per year for patients with diabetes type 2 and four times per year for patients
 476 with diabetes type 1. If the patient has specific problems variables may be recorded with higher frequency.
 477 BMI: body mass index; HbA1: Haemoglobin subunit alpha 1; LDL: low density lipoprotein, HDL: high density
 478 lipoprotein; eGFR: estimated glomerular filtration rate

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3 479 **Figure 1.** The data linkage process. Data from the four national quality registers Better Management of
4 480 Patients with Osteoarthritis Register (BOA), Swedish Hip Arthroplasty Register (SHAR), Swedish Knee
5 481 Arthroplasty Register (SKAR) and National Diabetes Register (NDR) is safely transferred to Statistics
6 482 Sweden. Statistics Sweden will anonymise the data by replacing PIN with serial numbers. Data will be
7 483 extracted from LISA (Longitudinal integration database for health insurance and labour market studies)
8 484 and transferred to the entity principally responsible for the Swedish Osteoarthritis and Diabetes (SOAD)
9 485 cohort research. The PIN and serial numbers will also be shared with National Board of Health and Welfare
10 486 who will return data from National Patient Register (NPR), Swedish Prescribed Drug Register (SPDR), Cause
11 487 of Death Register (CODR) and Swedish Cancer Register (SCR) to the entity principally responsible for the
12 488 research. The linkage key will be saved at Statistics Sweden for 3 years to allow the possibility of adding
13 489 more year cohorts or new variables to the research database if new research questions arise (with new
14 490 ethical approval).
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The data linkage process. Data from the four national quality registers Better Management of Patients with Osteoarthritis Register (BOA), Swedish Hip Arthroplasty Register (SHAR), Swedish Knee Arthroplasty Register (SKAR) and National Diabetes Register (NDR) is safely transferred to Statistics Sweden. Statistics Sweden will anonymise the data by replacing PIN with serial numbers. Data will be extracted from LISA (Longitudinal integration database for health insurance and labour market studies) and transferred to the entity principally responsible for the Swedish Osteoarthritis and Diabetes (SOAD) cohort research. The PIN and serial numbers will also be shared with National Board of Health and Welfare who will return data from National Patient Register (NPR), Swedish Prescribed Drug Register (SPDR), Cause of Death Register (CODR) and Swedish Cancer Register (SCR) to the entity principally responsible for the research. The linkage key will be saved at Statistics Sweden for 3 years to allow the possibility of adding more year cohorts or new variables to the research database if new research questions arise (with new ethical approval).

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1-2	
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5	
Objectives	3	State specific objectives, including any prespecified hypotheses	5	
Methods				
Study design	4	Present key elements of study design early in the paper	6-8	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8	
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	7-8	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9, table 5	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Table 1 to 4	
Bias	9	Describe any efforts to address potential sources of bias	9	
Study size	10	Explain how the study size was arrived at	7-8 (BOA), 8 (other registers) 10	

			(sample size), Figure 1 (merging process)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9
		(b) Describe any methods used to examine subgroups and interactions	9
		(c) Explain how missing data were addressed	9
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	9
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N/A
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	N/A
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	N/A
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	N/A
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(b) Report category boundaries when continuous variables were categorized	N/A
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	N/A
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	N/A
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	N/A
Generalisability	21	Discuss the generalisability (external validity) of the study results	N/A
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.