SUPPLEMENTAL MATERIAL

Exploring heterogeneity in coxarthrosis medication use patterns before total hip replacement: a State Sequence Analysis

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Contents

1. List of codes used for data preparation and analysis

1.1 Study Population

We defined the study population based on the following codes:

- Coxarthrosis diagnosis: ICD-10 code M16
- Exclusion of patients diagnosed with femur fractures, femoral osteonecrosis, or complications from orthopedic devices: ICD-10 codes S72, M87.05, M87.15, M87.25, M87.35, M87.85, M87.95, T84
- Total Hip Replacement (THR) surgery: OPS code 5-820

1.2 Medication States

The definition of medication states aligns with the WHO's analgesic ladder [1]. Medication state M corresponds to mild analgesics of stage 1 of the WHO analgesic ladder. State O corresponds to mild and strong opioids of stages 2 and 3 of the same ladder. Medications were identified in the data using codes from the Anatomical Therapeutic Chemical (ATC) Classification. For the list of ATC-codes, please refer to Table 1.

1.3 Physical therapy

The *physical therapy* variable represents the utilization of any therapies listed in the German 'Heilmittelkatalog' (Catalogue of Therapeutic Products) during the observation period. These therapies were identified by their respective 'Leistungsart' (type of service) codes:

- Motion Therapy/Physiotherapy: 03, 04, 05, 06, 07, 08, 09, 10, 62, 63
- Massage: 01, 60
- Manual Lymphatic Drainage: 02, 61
- Manual Therapy: 12
- Extension/Traction Treatment: 11, 64
- Electrotherapy: 13, 65
- Hydrotherapy: 16, 67

1.4 Hierarchical pain categories

The variable *pain* aims to identify patients experiencing discomfort based on their health conditions as reflected by their ICD-diagnoses. This is crucial, given that the prescriptions used to define pain medication use do not provide the reason for the prescription. Therefore, conditions other than coxarthrosis that also cause pain can influence the use of pain medication. In our analysis, we use a hierarchical categorical

Table 1. ATC codes used for the definition of medication states

ATC code	name
WHO stage 1: mild analgesics	
N02B	Other analgesics and antipyretics
M01A	Anti-inflammatory and antirheumatic products, non-steroids
M01B	Antiinflammatory/antirheumatic agents in combination
WHO stage 2: weak opioids	
N02AX01	Tilidine
N02AX51	Tilidine and naloxone
N02AX02	Tramadol
N02AX52	Tramadol and paracetamol
N02AA08	Dihydrocodein
N02AA58	Dihydrocodeine, combinations
N02AA59	Codeine, combinations excl. psycholeptics
N02AA65	Codeine combination with diclofenac
N02AA66	Codeine combination with acetyleic acid
N02AA69	Codeine combination with paracetamol
N02AA62	Tramadol combination with paracetamol
WHO stage 3: strong opioids	
N02AA01	Morphin
N02AA51	Morphine, combinations
N02AA03	Hydromorphone
N02AA05	Oxycodone
N02AA55	Oxycodone, combinations
N02AA25	Oxycodon and naloxone
N02AF01	Butorphanol
N02AB02	Pethidine
N02AB03	Fentanyl
N02AC03	Piritramide
N02AC06	Levomethadon
N02AE01	Buprenorphine
N02AE02	Buprenorphine
N02AX06	Tapentadol
N02AX06	Tapentadol

Medication state M corresponds to WHO stage 1, while state O includes WHO stages 2 and 3.

variable with four levels, with the base level representing coxarthrosis and conditions assumed to cause comparable pain, and three additional levels depicting conditions associated with higher pain severity. Since a coxarthrosis diagnosis was a criterion used to define our study population, all the patients in our analysis inherently belong at least to the coxarthrosis pain category.

For defining the pain variable, we adapted the method utilized by Freytag et al. [2]. The researchers developed a group of diagnoses arranged into nine hierarchical pain categories aimed at identifying and sorting pain patients within insurance claim data. The ICD codes for pain categories equivalent or superior to the pain level of coxarthrosis are presented in Table 2. We adapted the cancer category slighlty by not including all subcategories of ICD-10 code Z51 - 'Other medical care', due to its broad and vague scope. We incorporated only Z51 diagnoses pertinent to cancer treatment while excluding others (see Table 2).

Table 2. ICD-10 codes for the four highest pain categories as defined by Freytag et al. [2, p.18-20, Tab.3-7]

Pain category 1: "Pain associated with cancer"	
Z51	Other medical care*
C80	Malignant neoplasm, without specification of site
C78	Secondary malignant neoplasm of respiratory and digestive organs
C77	Secondary and unspecified malignant neoplasm of lymph nodes
C79	Secondary malignant neoplasm of other and unspecified sites
C34	Malignant neoplasm of bronchus and lung
C20	Malignant neoplasm of rectum
C90	Multiple myeloma and malignant plasma cell neoplasms
C64	Malignant neoplasm of kidney, except renal pelvis
C85	Other and unspecified types of non-Hodgkin lymphoma
Pain category 2: "Other specific back pain, including osteoporosis, excluding disc disorders"	
M48	Other spondylopathies
M81	Osteoporosis without pathological fracture
M46	Other inflammatory spondylopathies
M45	Ankylosing spondylitis
M43	Other deforming dorsopathies
M82	Osteoporosis in diseases classified elsewhere
M49	Spondylopathies in diseases classified elsewhere
Pain category 3: "Pain associated with disc disorders"	
M51	Other intervertebral disc disorders
M50	Cervical disc disorders
Pain category 4: "Pain associated with ostheoarthritis inkluding rheumatoid arthritis" †	
M17	Gonarthrosis [arthrosis of knee]
M16	Coxarthrosis [arthrosis of hip]
M19	Other arthrosis
M15	Polyarthrosis
M25	Other joint disorders, not elsewhere classified
M13	Other arthritis
M06	Other rheumatoid arthritis
M18	Arthrosis of first carpometacarpal joint

Please refer to Freytag et al [2] for full code set and all pain categories. * We only included subdiagnoses of ICD Z51 that are correlated to cancer treatment and excluded codes that were considered very broad or vague. Subcodes included are: Z51.0 Radiotherapy session, Z51.1 Chemotherapy session, Z51.2 Other chemotherapy, Z51.5 Palliative care, Z51.82 Combined radiotherapy and chemotherapy session for malignant neoplasm. Subcodes excluded are: Z51.3 Blood transfusion (without reported diagnosis), Z51.4 Preparatory care for subsequent treatment, not elsewhere classified, Z51.6 Desensitization to allergens, Z51.81 Apheresis, Z51.83 Opioid substitution, Z51.88 Other specified medical care, Z51.9 Medical care, unspecified. † ICD codes of Pain category 4 were not actually used for the pain variable employed in our analysis, since all patients of our study population have coxarthrosis and belong at least to this category.

1.5 Other patient characteristics

The variable *opioid dependency* was defined as being diagnosed with one of the following ICD-10 codes: F11, T40.0, T40.1, T40.2, T40.3. The variable *vertigo* was defined as being diagnosed with one of the following ICD-10 codes: H81, H82, R42, A881.

2. Cluster analysis

2.1 State dissimilarity and sequence dissimilarity

Sequence clustering relies on the definition of a measure of sequence (dis-)similarity. It requires the definition of when two objects, or sequences, are considered similar or, conversely, dissimilar. We used optimal matching (OM) to create a dissimilarity matrix that is generated by summing the cost of the operations necessary to transform one sequence into the other. The three basic operations are insertion, deletion (always in combination, also referred to as "indel") and substitution. In general, indels warp time and affect the contemporaneity of sequences, while substitutions alter states. Substitution costs may follow a theory-driven approach or a data-driven approach, commonly using transition rates between states. When applied outside the field of microbiology, the data-driven approach has been criticized for a lack of interpretability [3] and for the inability of state transitions to reflect state similarities [4]. Hence, we predicated our substitution costs on state features that reflect the hierarchy of the defined states.

We created a minimal feature dataset that encapsulates the hierarchy of the states, mirroring the hierarchy of the WHO's analgesic ladder [1]:

$$\begin{pmatrix} \text{state N} \\ \text{state M} \\ \text{state O} \end{pmatrix} \hat{=} \begin{pmatrix} 0 \\ 1 \\ 2 \end{pmatrix} \tag{1}$$

We computed the Gower distances based on this feature dataset using the seqcost-function from the TraMineR package [5] [6]. This resulted in the following substitution cost matrix sm:

$$\text{sm} = \begin{pmatrix} & \text{state N} & \text{state M} & \text{state O} \\ \text{state N} & 0 & 0.5 & 1 \\ \text{state M} & 0.5 & 0 & 0.5 \\ \text{state O} & 1 & 0.5 & 0 \end{pmatrix} \tag{2}$$

As highlighted by the substitution cost matrix, grounded on the hierarchical feature dataset, state N and state O (substitution cost=1) demonstrate greater dissimilarity than state M and state O (substitution cost=0.5). This aligns with our intuitive understanding of how medication states should correlate with one another.

For the indel costs, we adhered to the default approach [4], setting the indel cost equivalent to half the maximum substitution cost, thus at 0.5.

2.2 Clustering

We used a partitioning around medoids algorithm (PAM) and performed clustering for different values of k, the number of initial medoids (k between 2 and 15) and thus the number of clusters.

2.3 Choise of cluster solution

To determine the optimal number of clusters, we conducted an assessment employing various quality criteria, namely:

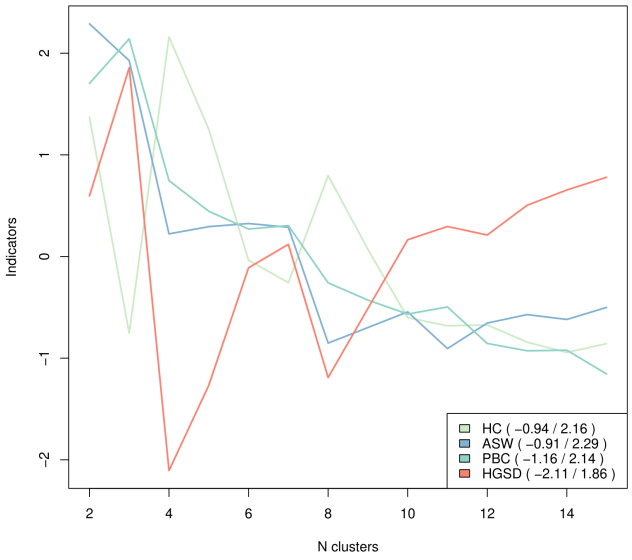

Figure 1. Graphical depiction of normed cluster quality indicators Hubert's C (HC), Hubert's Somers' D (HGSD), Average Silhouette Width (ASW), and Point Biserial Correlation (PBC) for clustering solutions with cluster count (N) ranging from 2 to 15.

- Average Silhouette Width (ASW), which signifies the homogeneity within a cluster and heterogeneity across clusters,
- Point Biserial Correlation (PBC), and
- Hubert's Somers' D (HGSD), both of which gauge the ability of the clustering method to replicate the original distances,
- Hubert's C (HC), which evaluates the variance between the derived partition and the optimal partition, assuming the same group count.

Our selection of these criteria draws on the work of Studer et al., 2013, which provides a compilation of quality parameters suitable for the evaluation of sequence clustering [7]. From this collection, we selected the criteria most pertinent to our analysis, specifically for evaluating partitions of varying sizes obtained through an optimal matching and non-Euclidean distance-based clustering technique.

The desired cluster solutions are those for which the quality criteria register high values for ASW, PBC, and HGSD, and low values for HC [7]. Our analysis extended to a 15-cluster solution. We decided against larger cluster numbers, as

these tend to be overwhelming and lose their relevance in studying the patient population. An excessive cluster count is also more likely to induce overclustering, leading to the identification of minor and inconsequential patterns specific to the dataset, rather than broad, general patterns likely to surface in comparable study populations.
Figure 1 illustrates the cluster quality indicators for clustering solutions with cluster counts extending from 2 to 15. All quality parameters exhibit a progressive increase/decrease beginning at around the 9-cluster solution, a characteristic trend signifying overclustering. This implies our potential solution lies within the 2 to 9-cluster range. At the 3-cluster solution, we observe a HC minimum (0.026), an HGSD maximum (0.96), a PBC maximum (0.76), and a high ASW value (0.64, with the maximum at the 2-cluster solution being 0.66). Another notable solution presents at the 7-cluster solution, where we observe the second lowest value and local minimum for HC (0.032). The silhouette remains relatively high, plateauing between the 4 and 7-cluster solutions (0.52) before dropping significantly beyond the 7-cluster solution. The PBC exhibits a small local maximum at the 7-cluster solution (0.64), subsequently dropping beyond this point. The HGSD registers the second highest value and local maximum at the 7-cluster solution (0.92), making it a potential candidate. When comparing the 7 and 3-cluster solutions (please refer to figure 2), it is evident that the patterns of the 3-cluster solution are encapsulated within the 7-cluster solution (Clusters N, M, and High-O). Furthermore, the sensitivity analyses have validated the stability of the 7-cluster solution's patterns (see section 2.4 and Figure 3). Consequently, we opted for the more granular 7-cluster solution for our primary analysis.

2.4 Sensitivity analysis

To ensure the robustness of the emergent clusters or patterns, we conducted numerous sensitivity analyses, each employing a unique study population. As detailed in the manuscript, this population comprised a group of 9,975 patients who underwent hip replacement surgery (THR group) and a similarly sized group of patients who did not undergo THR (noTHR group). Initially, 117,570 patients were eligible for the noTHR group, from which 9,975 were selected at random. This random selection process was repeated in each sensitivity analysis. The re-drawing of the patient population was not an option for the THR group, as it included all patients from the dataset who underwent surgery. Nevertheless, we implemented sensitivity analyses where the noTHR group was created from a bootstrapped sample. In each analysis, the same parameters were used for cluster analysis, following which we computed the quality criteria for clustering, mirroring our main analysis. Many of the sensitivity analyses indicated a 7-cluster solution based on the quality criteria, though a local maximum for the 8-cluster solution was found in some cases. Figure 3 illustrates the outcomes of three distinct sensitivity analyses. Sensitivity analyses 1 and 2 utilized a dataset with a newly random drawn population for the noTHR group, maintaining the same THR group as the primary analysis. Sensitivity analysis 3 shows the result of clustering a dataset with a newly random drawn noTHR group and a bootstrapped THR group. The figure compellingly attests to the stability of the patterns, as similar clusters with comparable sizes consistently emerge across all analyses. Notably, clusters N, Cluster Increase, Cluster M, and Cluster High-O consistently appear with remarkable clarity. Additionally, two M-peak clusters are invariably identified, albeit with the peak manifesting in varying months—a logical occurrence if this pattern is attributable to a severe phase of chronic coxarthrosis. In Sensitivity analysis 3, the Medium-O cluster is likely largely subsumed within High-O, which might also elucidate the marginally lower opioid level in High-O observed in this analysis. Furthermore, another cluster with increasing state M rates is discernible in the presented sensitivity analyses, albeit its form appears somewhat variable. At times, peaks reminiscent of the M-peak clusters are again apparent, as well as an increase in medication usage toward the end of the observation period, analogous to the pattern observed in Cluster Increase. Overall, the striking similarity across the solutions confirms the stability of the identified patterns.

3. Theoretical model informing logistic regression

In order to inform the logistic regression, a theoretical model was developed, utilizing directed acyclic graphs (DAGs). The adoption of DAGs offers a systematic strategy to minimize potential biases when assembling regression models, as delineated by Shrier and Platt (2008) [8]. For a comprehensive overview of the methodological framework regarding DAGs, we recommend the aforementioned reference.
To build our model, we used DAGitty, a browser-based platform designed for developing and illustrating causal diagrams. DAGitty can be accessed at dagitty.net. The resulting model is shown in Figure 4.

3.1 Building the model

The subsequent text provides rationale for the inclusion of variables in our theoretical model.
Our primary interest lies in the total effect of the medication cluster on the incidence of total hip replacement. Thus, we introduced *medication cluster* as an exposure variable and *surgery* as an outcome variable.
Accounting for a patient's comorbidity is essential when analyzing healthcare usage and decision-making patterns. We introduced *comorbidity* as an unobserved variable to represent true comorbidity, recognizing that our dataset lacks comprehensive measures to fully capture a patient's comorbidity spectrum. As an alternative, we incorporated several relevant measures into our model, each offering different yet complementary insights into a patient's comorbidity.

- We computed the van Walraven-Elixhauser score (*Elixhauser score*), an index of general comorbidity, based on the primary hospital diagnoses during the observation period (range: $[-19; 89]$, with higher scores signifying greater severity of comorbidity) [9, 10]. The Elixhauser

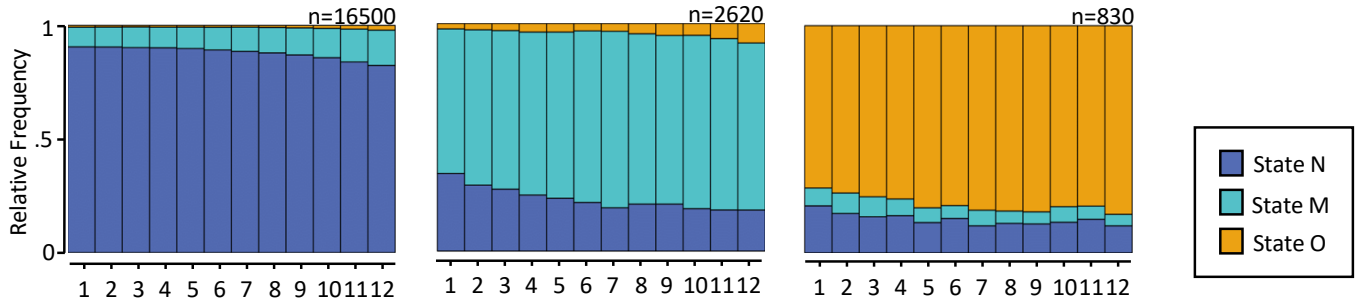

Figure 2. Distribution plots illustrating the 3-cluster solution. The patterns within these three clusters align closely with those observed in clusters N, M, and High-O from the primary analysis.

score has been validated as superior to other comorbidity measures for administrative data [e.g. 11, 12]. Comorbidity has been correlated with THR surgery [13].

- A hierarchical variable *pain>coxarthrosis* was introduced into the model to adjust for pain symptoms, as elaborated in section 1.4 of this document. The rationale behind this inclusion is the observed correlation between experiencing pain and the utilization of pain medication[2]. We incorporated pain categories exceeding the pain level at which coxarthrosis is diagnosed, thus implying more severe pain. This variable is based on ICD-diagnoses in the claims database and is thus a specific aspect of the patient's comorbidity and is correspondingly connected to the unobserved comorbidity in the model. Considering that some diagnoses in the cancer pain category are part of the Elixhauser score as well, these two variables are interconnected.

- Given that opioids constitute one of the states considered in our analysis, we adjusted for *opioid dependency*. As ICD-code F11 is part of the Elixhauser score as well, we highlighted this correlation in the model.

- Lastly, we introduced *vertigo* into the model. Vertigo, a condition with many potential causes, mirrors a unique facet of the unobserved comorbidity. Notably, vertigo is a common side-effect of pain medication [14]. Vertigo/Dizziness could influence the decision to undergo THR due to patients' increased fear of falling [15].

We incorporated patient demographic characteristics such as age, gender, and the urbanity level of their residence area, and marked their well-known correlation with comorbidity in the model. Age and gender have been shown to influence the use of pain medication and physiotherapy [16, 17]. The rurality of a region impacts the local health care infrastructure [18], thereby affecting the accessibility, and consequently the use of health care services. Physiotherapy, an integral part of conservative therapy, is recommended to coxarthrosis patients prior to undergoing THR surgery [e.g. 19].
Finally, in an effort to achieve a comprehensive representation, and considering their significance in the decision-making process for THR, we incorporated the following unobserved factors into the model: pain experienced due to coxarthrosis (*pain (coxarthrosis)*) and radiological evidence of joint deterioration (*joint deterioration*). These factors are main criteria in the decision to undergo surgery [19, 20, 21]. However, neither of these factors can be depicted in health insurance claims data. It can be reasonably assumed that the pain experienced due to coxarthrosis affect the decisions regarding the use of pain medication and physiotherapy.
According to the presented DAG model, the minimal set of variables sufficient for estimating the total effect of *medication cluster* on *surgery* comprises the following factors: *Elixhauser score, age, opioid dependence, pain>ostheoarthritis, physiotherapy, sex, urbanity*. Consequently, we have included these variables as dependent factors in our logistic regression.

3.2 DAG code

Subsequently, we provide the code necessary for replicating this model on dagitty.net:

```
dag {
"Elixhauser score" [pos="-0.430,-0.650"]
"joint degeneration" [latent,pos="-0.081,1.658"]
"medication cluster" [exposure,pos="-0.758,0.442"]
"opioid dependence" [pos="-0.108,-0.549"]
"pain (coxarthrosis)" [latent,pos="-0.067,1.333"]
"pain>ostheoarthritis" [pos="-0.764,-0.725"]
age [pos="-1.638,1.337"]
comorbidity [latent,pos="0.360,-1.412"]
physiotherapy [pos="-0.755,1.197"]
sex [pos="-1.444,1.500"]
surgery [outcome,pos="0.551,0.442"]
urbanity [pos="-1.792,1.166"]
vertigo [pos="0.233,-0.443"]
"Elixhauser score" -> "medication cluster"
"Elixhauser score" -> "opioid dependence" [pos="0.064,-0.989"]
"Elixhauser score" -> "pain>ostheoarthritis" [pos="-0.318,-
0.967"]
"Elixhauser score" -> surgery
"joint degeneration" -> surgery
"medication cluster" -> surgery
"medication cluster" -> vertigo
"opioid dependence" -> "medication cluster"
"pain (coxarthrosis)" -> "medication cluster"
"pain (coxarthrosis)" -> physiotherapy
"pain>ostheoarthritis" -> "medication cluster"
age -> "joint degeneration"
age -> "medication cluster"
age -> comorbidity [pos="-1.694,-1.312"]
```

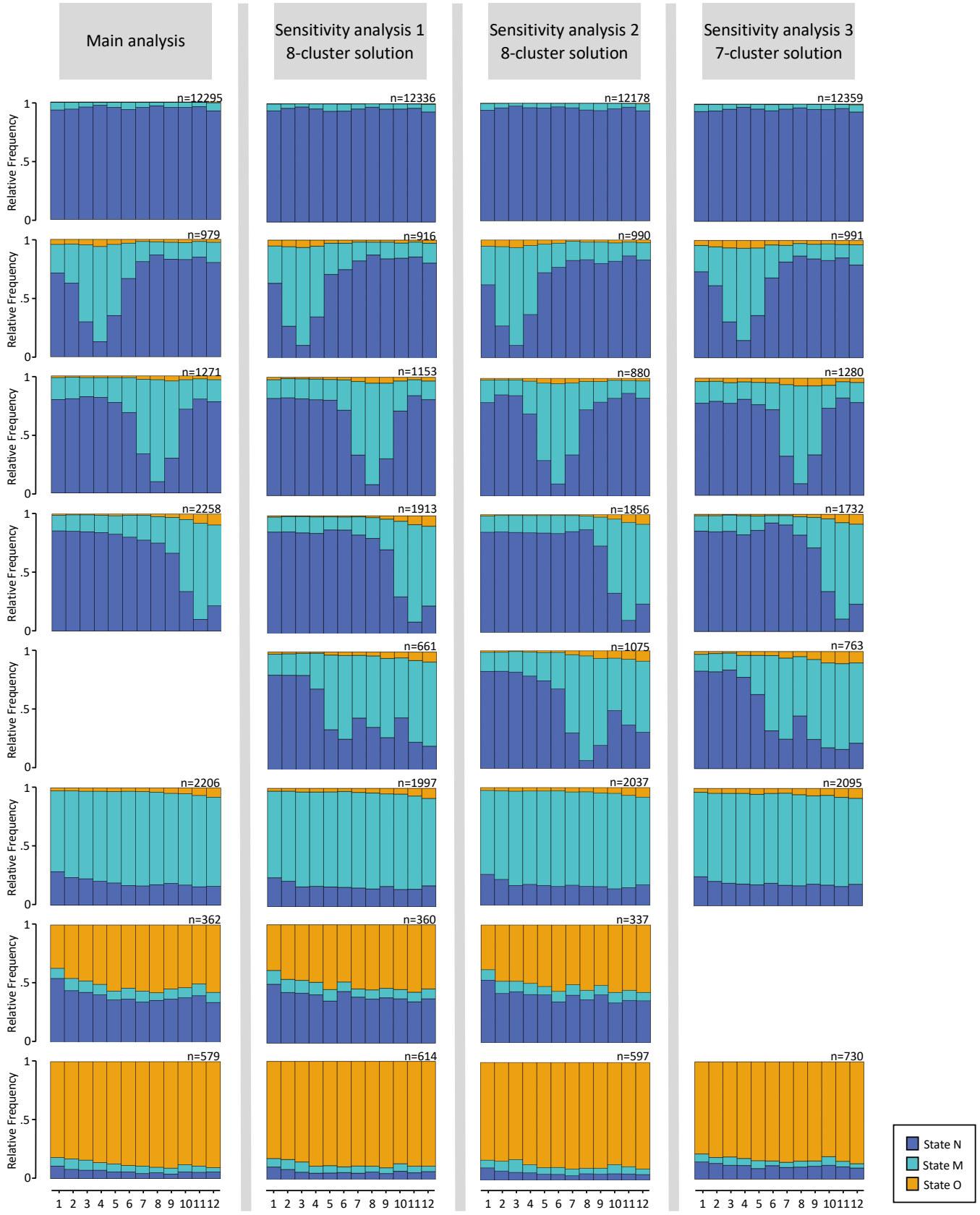

Figure 3. Outcomes of Selected Sensitivity Analyses: Sensitivity analyses 1 and 2 feature newly randomized population for the noTHR group, while Sensitivity analysis 3 incorporates both a re-randomized noTHR group and a bootstrapped THR group. The striking congruity across the cluster solutions underscores the robustness of the identified patterns.

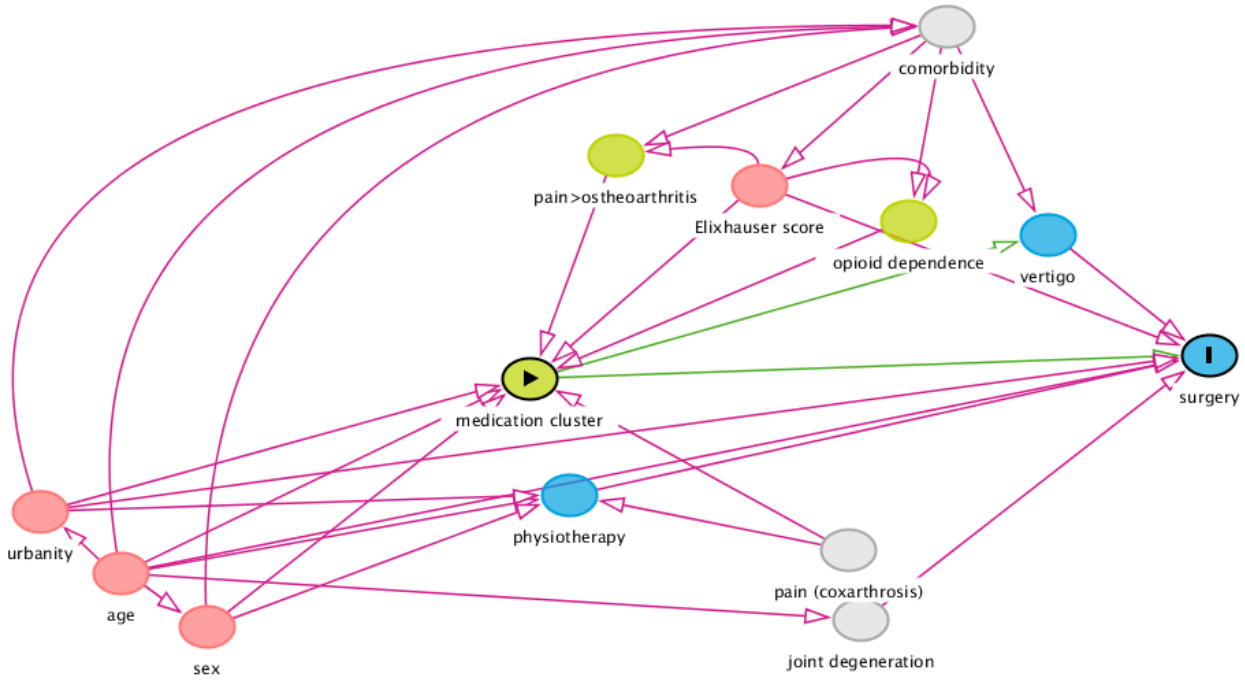

Figure 4. Theoretical model informing logistic regression using directed acyclic graphs (DAG). The figure was generated using dagitty.net [22]. Red nodes denote ancetors of exposures and outcome, yellow nodes ancestors of exposure, blue nodes, ancestor of outcomes, grey nodes unobserved variables. Red paths denote biasing paths, green paths causal paths. The yellow triangle marked node denotes the exposure variable, the blue node marked with a line denotes the outcome variable.

```
age -> physiotherapy
age -> sex
age -> surgery
age -> urbanity
comorbidity -> "Elixhauser score"
comorbidity -> "opioid dependence"
comorbidity -> "pain>ostheoarthritis"
comorbidity -> vertigo
physiotherapy -> surgery
sex -> "medication cluster"
sex -> comorbidity [pos="-1.394,-1.235"]
sex -> physiotherapy
urbanity -> "medication cluster"
urbanity -> comorbidity [pos="-1.981,-1.348"]
urbanity -> physiotherapy
urbanity -> surgery
vertigo -> surgery
}
```

References

[1] World Health Organization. Cancer pain relief, 1986. URL `https://apps.who.int/iris/bitstream/handle/10665/43944/9241561009_eng.pdf?sequence=1&isAllowed=y`.

[2] A. Freytag, G. Schiffhorst, R. Thoma, et al. Identifikation und Gruppierung von Schmerzpatienten anhand von Routinedaten einer Krankenkasse. *Schmerz*, 24:12–22, 2010. doi: 10.1007/s00482-009-0861-y.

[3] Cees H. Elzinga and Matthias Studer. Spell Sequences, State Proximities, and Distance Metrics. *Sociol. Methods Res.*, 44 (1):3–47, 2015. doi: 10.1177/0049124114540707.

[4] Matthias Studer and Gilbert Ritschard. What matters in differences between life trajectories: a comparative review of sequence dissimilarity measures. *Journal of the Royal Statistical Society: Series A (Statistics in Society)*, 179(2): 481–511, 2016. ISSN 1467-985X. doi: 10.1111/rssa.12125.

[5] Alexis Gabadinho, Gilbert Ritschard, Nicolas S. Müller, and Matthias Studer. Analyzing and Visualizing State Sequences in R with TraMineR. *Journal of Statistical Software*, 40(4): 1–37, 2011. doi: 10.18637/jss.v040.i04.

[6] J. C. Gower. A General Coefficient of Similarity and Some of Its Properties. *Biometrics*, 27(4):857, 1971. doi: 10.2307/2528823.

[7] Matthias Studer. WeightedCluster Library Manual: A practical guide to creating typologies of trajectories in the social sciences with R. *LIVES Working Papers*, 2013:1–32, 2013. ISSN 2296-1658. doi: 10.12682/lives.2296-1658.2013.24.

[8] I. Shrier and R.W. Platt. Reducing bias through directed acyclic graphs. *BMC Med Res Methodol*, 8(70):81–86, 2008. doi: 10.1186/1471-2288-8-70.

[9] A. Elixhauser, C. Steiner, D. R. Harris, and R. M. Coffey. Comorbidity measures for use with administrative data. *Med Care*, 36(1):8–27, 1998. doi: 10.1097/00005650-199801000-00004.

[10] Carl van Walraven, Peter C. Austin, Alison Jennings, Hude Quan, and Alan J. Forster. A modification of the Elixhauser comorbidity measures into a point system for hospital death using administrative data. *Med. Care*, 47(6):626–633, 2009. doi: 10.1097/MLR.0b013e31819432e5.

[11] Nathaniel T. Ondeck, Daniel D. Bohl, Patawut Bovonratwet, Ryan P. McLynn, Jonathan J. Cui, and Jonathan N. Grauer. Discriminative ability of elixhauser's comorbidity measure is superior to other comorbidity scores for inpatient adverse outcomes after total hip arthroplasty. *The Journal of Arthroplasty*, 33(1):250–257, 2018. ISSN 0883-5403. doi: https://doi.org/10.1016/j.arth.2017.08.032. URL https://www.sciencedirect.com/science/article/pii/S0883540317307556.

[12] M.C.S. Inacio, N.L. Pratt, E.E. Roughead, and S.E. Graves. Evaluation of three co-morbidity measures to predict mortality in patients undergoing total joint arthroplasty. *Osteoarthritis and Cartilage*, 24(10):1718–1726, 2016. ISSN 1063-4584. doi: https://doi.org/10.1016/j.joca.2016.05.006. URL https://www.sciencedirect.com/science/article/pii/S1063458416300826.

[13] Toni Lange, Andres Luque Ramos, Katinka Albrecht, Klaus-Peter Günther, Hannes Jacobs, Jochen Schmitt, Falk Hoffmann, Jens Goronzy, and Anne Postler. Verordnungshäufigkeit physikalischer Therapien und Analgetika vor dem Einsatz einer Hüft- bzw. Kniegelenks-Endoprothese. *Orthopäde*, 47: 1018–1026, 2018. doi: 10.1007/s00132-018-3629-1.

[14] R. Benyamin, A. M. Trescot, S. Datta, R. Buenaventura, R. Adlaka, S. E. Sehgal N., Glaser, and R. Vallejo. Opioid complications and side effects. *Pain Physician*, 11(2 Suppl): 105–120, 2008.

[15] C. Schlick, R. Schniepp, V. Loidl, M. Wuehr, K. Hesselbarth, and K. Jahn. Falls and fear of falling in vertigo and balance disorders: A controlled cross-sectional study. *Journal of Vestibular Research*, 25(5-6):241–251, 2015.

[16] Sussmann KE, Jacobs H, and Hoffmann F. Physical Therapy Use and Associated Factors in Adults with and without Osteoarthritis—An Analysis of the Population-Based German Health Update Study. *Healthcare*, 9(11):1544, 2021. doi: 10.3390/healthcare9111544.

[17] E. Hradetzky, C. Ohlmeier, C. Brinkmann, M. Schild, W. Galetzka, N. Schmedt, T. John, D. Kaleth, and H. Gothe. Epidemiology and routine care treatment of patients with hip or knee osteoarthritis and chronic lower back pain: real-world evidence from germany. *Journal of Public Health*, 30(12): 2855–2867, 2022. doi: 10.1007/s10389-022-01700-8.

[18] Verena Vogt. The contribution of locational factors to regional variations in office-based physicians in germany. *Health Policy*, 120(2):198–204, 2016. doi: https://doi.org/10.1016/j.healthpol.2016.01.006.

[19] Deutschen Gesellschaft für Orthopädie und Orthopädische Chirurgie (DGOOC) und des Berufsverbandes der Ärzte für Orthopädie (BVO). S3-Leitlinie Koxarthrose, 2009.

[20] Deutsche Gesellschaft für Unfallchirurgie. S1-Leitlinie Endoprothese bei Koxarthrose, 2008.

[21] Deutsche Gesellschaft für Orthopädie und Orthopädische Chirurgie (DGOOC). Evidenz- und konsensbasierte Indikationskriterien zur Hüfttotalendoprothese bei Coxarthrose (EKIT-Hüfte), Version 1.0, 2021. URL https://www.awmf.org/leitlinien/detail/ll/187-001.html.

[22] Johannes Textor, Benito van der Zander, Mark S Gilthorpe, Maciej Liśkiewicz, and George TH Ellison. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. *International Journal of Epidemiology*, 45(6):1887–1894, 01 2017. doi: 10.1093/ije/dyw341.