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Identifying and investigating empirical patient-pathways

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Table of contents

List of abbreviations

CA Coronary angiography
CAD Coronary Artery Disease
DMP Disease Management Program
NID Non-invasive diagnostics
SSA State Sequence Analysis
THR Total hip replacement
WHO World Health Organization

1 Introductory summary

1.1 Empirical patient pathways

Protocols, routines, guidelines, and flowcharts are an integral part of everyday clinical practice and are widely used in healthcare [1, 2]. These management tools, which are referred to as structured care methodologies [1, 3], are used to standardize and optimize care processes, reduce treatment errors, and improve patient outcomes and cost-effectiveness [4, 5]. They manage small organizational units such as emergency rooms or physician's offices, as well as larger systems such as entire hospitals. Some programs adopt an even broader scope and incorporate transitions between different provider specialties and between the outpatient and inpatient sectors. In Germany, for instance, Disease Management Programs (DMP) have been developed for many chronic conditions, such as type 2 diabetes, chronic heart disease, and asthma [6]. Another prominent example of structured care methodologies are treatment guidelines. Over the past decades, professional organizations worldwide have continuously developed treatment guidelines for an increasing number of conditions, aiming to synthesize and summarize evidence and to provide guidance for medical professionals and patients [e.g. 7–9].

Treatment guidelines and other structured care methodologies have an inherent normative character: They show how patients *should* be treated, which healthcare services they *should* receive, and aim to outline or define an 'ideal care path'. While we have, for many conditions, a well-defined idea of how this ideal care path should look like, research on geographic variation in the utilization of healthcare services reveals that variation in treatment exists and that patients do not navigate the healthcare system uniformly [10–13]. In recent years, researchers began to investigate how individual patient pathways *actually* unfold and how patients *truly* navigate the healthcare system [14–16]. Instead of focusing on the ideal path, the aim is to identify, visualize, explore, and investigate real-world, empirical patient pathways. By 'empirical patient pathway', we understand the sequential series of healthcare services that a patient receives over a defined time period. These pathways often deviate – sometimes substantially – from the ideal paths outlined in treatment guidelines. Such deviations can arise due to various factors, including supply-side influences

(e.g., medical practice variation, provider preferences, and regional availability of services) and patient-side factors (e.g., health literacy, socioeconomic status, and individual preferences) [e.g. 17, 18].
The study of empirical patient pathways promises several kinds of knowledge gain [15]:

1. A holistic understanding of how patients actually navigate through the healthcare system. This often includes efforts to capture the plethora of diverse pathways through visualizations.

2. An understanding of why patients follow certain pathways. Correlation analyses of pathways with patient characteristics, regional factors, and supply-side factors help to understand the context in which pathways emerge.

3. Identification of deviations from treatment guidelines and care gaps. By comparing patient pathways with recommendations from treatment guidelines, deviations and unaddressed care needs can be identified.

4. An understanding of how these pathways might impact patients' health. This includes correlation analyses of pathways with health outcomes.

Results from empirical patient pathway analyses provide detailed and comprehensive insight into care processes of patient populations and highlight treatment gaps and deviations from guideline recommendations [e.g. 19–21]. Such findings can inform health policy and decision-making. Ultimately they can be used to optimize and redesign normative care pathways or programs, thereby improving healthcare and enhancing cost-efficiency [14, 22, 23]. Additionally, analyses of patient pathways can pinpoint areas for future research.

1.2 Health insurance claims data

Comprehensive, longitudinal datasets are essential for studying empirical patient pathways. To accurately capture the trajectories of patients across the healthcare system, such datasets must cover multiple providers and sectors over relevant time periods. Recent advances in digitization have led to the creation of large amounts of data in all aspects of life, often referred to as a 'data explosion' [24]. Similarly, in

the healthcare sector, large volumes of data are now being accumulated, including health insurance claims, electronic health records, hospital records, imaging data, as well as information from wearables and fitness devices [25]. In Germany, health insurance claims data have increasingly been used for research [26]. These datasets typically provide basic demographic information, diagnoses, medication prescriptions, information on laboratory tests, medical procedures, physician visits, and hospitalizations [26, 27]. Statutory regulations ensure data standardization across different insurance providers [28]. The main drawback, however, stems from the fact that the data were collected for billing purposes rather than for research. This necessitates careful operationalization of populations, events, and diseases, often relying on surrogate parameters [26]. Moreover, the data offer only limited clinical detail: while a laboratory test is recorded in the data, the result of the test remains unknown. Medical information such as blood pressure, weight, height, test results or X-rays are not included in claims data, to name a few important examples [26]. Yet, claims data are well-suited for patient pathway analysis because of their comprehensiveness, inclusion of large case numbers over extended periods of time, and relatively low selection bias [26].

1.3 Analytical methods to identify empirical patient pathways

Research on empirical patient pathways requires not only appropriate data but also robust analytical methods. Tracing a single patient's pathway based on their medical history, visualizing it, and comparing it to treatment recommendations may seem intuitive. However, extending these steps to entire populations implies handling numerous, possibly diverging pathways simultaneously. Extracting meaningful insights from this analysis is therefore both complex and challenging.

1.3.1 Knowledge discovery in databases

Parallel to the data explosion, interest and efforts grew to make this data usable and to develop methods that could extract meaningful information: The field of Knowledge Discovery in Databases (KDD) can be defined as the 'process of identifying valid, novel, potentially useful, and ultimately understandable structure in data' [29, 30,

p.41]. At the core of the KDD process is the step of data mining '(...) that enumerates structures (patterns or models) over the data' [29, 30, p.41]. Data mining encompasses a multitude of methods, including unsupervised learning algorithms [24]. In contrast to supervised learning, unsupervised learning deals with the extraction and identification of unknown data structures and patterns without knowledge of the outcomes a priori [24]. Therefore, these algorithms are particularly interesting for the identification of empirical patient pathways. In a comprehensive scoping review, Flothow, Novelli, Sundmacher (2023) [15], we explored algorithms and methods used to identify patient pathways from healthcare utilization data. In fact, 86% of the 51 included studies reported using unsupervised learning methods, with more than half of the studies reporting the use of a clustering algorithms [15]. Clustering algorithms are unsupervised learning methods that aim to group similar data objects by applying a predefined measure of similarity [24]. Other methods that were used include pattern mining techniques and Markov modeling, often in combination with clustering [15].

1.3.2 State Sequence Analysis

In recent years, sequence clustering methods, referred to as State Sequence Analysis (SSA), emerged in healthcare research [16]. SSA can be viewed as a comprehensive toolbox offering various options for operationalizing trajectories as sequences, visualizing these sequences, and clustering them. This makes SSA a promising approach for investigating individual trajectories within complex databases. Originating in sociology, SSA was initially developed for the study of life courses and stages [31–33]. The starting point of SSA involves operationalizing the states that represent the aspects we aim to study and from which we seek to identify patterns. For instance, in the context of employment trajectories, states might include 'employment', 'unemployment', and 'in training'. Once these states are defined, the observation period is divided into time units, and each individual in the study population is assigned to one of the predefined states for every time unit. The consecutive sequences of states across the observation period for each individual form the state sequences, which are the central objects of SSA. Once defined and operationalized in the data, they can be described and analyzed [33]. Also the visualization of sequences is an

integral part of SSA [19, 32, 33].
The analysis of state sequences generally involves two main steps. First, the pairwise similarity or dissimilarity between the sequences is measured. Second, these similarity measurements are used to perform a data reduction step, usually a clustering algorithm, to uncover patterns in the data [19, 33–35]. The choice of methods for both steps is crucial to the overall analysis [19, 33–35].
Over the last decades, SSA was not only increasingly used in its field of origin [33], but it has been adopted in the healthcare sector to investigate empirical patient pathways using insurance claims data: A recent review from the year 2024 [16] identified 19 studies that applied SSA to health insurance claims data, of which 84% (including one publication from this thesis [36]) were published in the last 5 years, i.e. during the timeframe of this PhD. One contributing factor for these developments is the availability of well documented and comprehensive software tools that facilitate such analyses [32, 37, 38].

1.4 Aim of this thesis

The aim of this thesis is to identify, visualize, and investigate empirical patient pathways in two different medical contexts using comprehensive health insurance datasets and employing novel methodological approaches.
First, we focus on patients with coronary artery disease (CAD). Central to our investigation is the procedure of invasive coronary angiography (CA), which has been debated in Germany for years due to its high rates compared to other countries [39–43] and significant regional variation within the country [12, 13], despite the existence of well-established treatment guidelines [44–46]. Assessing the appropriateness of medical indication for CA on a population level is challenging; instead, we aim to explore and better understand the healthcare context of patients leading up to the procedure. Specifically, we seek to identify and visualize typical ambulatory care pathways of the patients prior to undergoing CA and examine whether certain pathways are correlated with specific patient characteristics. Furthermore, we wish to investigate the extent to which the identified pathways reflect guideline recommendations, particularly regarding the role of general practitioners and specialists and the use of conservative medication therapies. By comparing the pathways with

guidelines, we seek to identify potential deviations from guidelines or gaps in care. Similar questions in a different medical context motivate our second paper, where we study a population of patients with coxarthrosis. In this study, we wish to investigate the pathways leading up to total hip replacement (THR) surgery. The appropriateness of the indication for THR and the potential influence of supply-side factors have been topics of discussion for decades, with high utilization rates and significant regional variation observed in Germany [11, 47–49]. This exploratory study aims to identify and visualize common medication patterns among coxarthrosis patients. We seek to investigate the correlation between these pathways and the occurrence of THR and to determine whether certain pathways lead to surgery. Additionally, we aim to assess the extent to which pathways reflect guideline-compliant use of pain medication and the extent to which medication therapy is exhausted in patients, who undergo surgery.

To identify and study the empirical patient pathways in both contexts, we apply the novel and promising sequence clustering method known as SSA.

In the following sections, I provide summaries of the two papers (sections 1.5, 1.6). For each paper, I outline the background and relevance of uncovering empirical patient pathways within the context of the studied patient population. I also present selected details on the data and methods, summarize the results, and interpret and discuss the identified care patterns. Discussion points regarding the method and the application of SSA are addressed collectively in an overarching section (section 1.7). This section explores methodological aspects, including the strengths and limitations of applying SSA in the two studies. Additionally, I offer an outlook on potential areas for future research before concluding this introductory summary.

1.5 Summary of Paper I: Ambulatory care sequences before invasive coronary angiography

Background In this study [36], we used SSA to shed light on the patients' pathways before undergoing CA. CA is a frequently performed procedure in patients with known or suspected CAD. Studies highlight that CA rates in Germany are not only high compared to other countries [39–43], but also exhibit considerable regional variation within Germany, that cannot be explained by morbidity differences in the population [12, 13]. Guidelines emphasize that CA should not be used as a standard diagnostic procedure in patients with stable CAD or suspected stable CAD, but non-invasive diagnostic methods (NID) such as coronary computer tomography should be used instead [44, 46]. CA should be only used if the patient considers revascularization therapy. Revascularization can be performed out of prognostic indication (Coronary Artery Bypass Graft), or out of symptomatic indication (Percutaneous Coronary Intervention) due to persistent symptoms after the exhaustion of conservative therapy. In this paper, we explored pathways of patients before undergoing CA with a particular focus on the use of conservative therapy options. We further investigated the occurrence of the discouraged medical practice of routinely performed follow-up CAs three to six months after revascularization therapy [50, 51].

Data and Methods We analyzed large health insurance claims data (2014 – 2017) from three German health insurances. The study population included 11,535 adults with known CAD who underwent CA in 2016. We used an observation time of 1.5 years, divided in 6 yearly quarters for pathway construction. To identify and investigate the pathways of patients we performed a SSA. Four care events, deemed relevant in the care for CAD and traceable in claims data, were selected, of which two focus on physician visits and two on drug prescriptions: consultation with a general practitioner (G), consultation with a cardiologist (C), prescription of prognosis-improving medication (P), and prescription of symptomatic medication (S). We based this categorization of conservative pharmacotherapy into prognosis-improving medication, which is recommended for every CAD patient, and symptom-improving medication, recommended depending on symptom level and comorbidities of the patient, on the national treatment guideline for stable CAD [44] and the work of Frank-

Tewaag et al. [52]. We defined 12 care states as combination of the four chosen care events (e.g. state GS: event G and S occurred during the time unit) and included additionally the null state N, which marks the state without any of the four events. Sequences were formed from these states, defined as the states the patients travel trough over the observation period. We used the Gower distance to calculate state similarity [35, 53] and used these state similarities within a localized optimal matching approach [35, 54] to calculate sequence similarity. Sequence clusters were identified with a partitioning around medoids algorithm [55]. The optimal number of clusters was determined using clustering quality criteria, primarily the average silhouette width, which measures inter-cluster heterogeneity and intra-cluster homogeneity [19, 35, 56, 57]. We visualized clusters and investigated them using descriptive statistics. To study the correlation of cluster membership with the occurrence of a routinely scheduled follow-up CA, we employed logistic regression.

Results Five distinct clusters were identified (average silhouette width = 0.35), with sizes ranging from 963 to 4,145 patients: *Cluster G*, dominated by state G; *Cluster Mix*, with states G and GPS being the most present states and increasing cardiologist consultations and medication use toward CA; *Cluster P*, dominated by state GP; *Cluster S*, dominated by state GS; *Cluster PS*, dominated by states GPS and GCPS. The dominant role of general practitioners was evident across all clusters, as each cluster's dominant states included event G. Cardiologist involvement was comparatively low overall, with the lowest cardiologist participation being observed in Cluster G, and the highest in Cluster Mix. Clusters differed notably in medication events. In Clusters Mix and PS (constituting 19.9% of the study population), most patients received both prognosis-improving and symptomatic medications in the last two quarters before CA. In contrast, in Clusters G and S (44.2% of the population), most patients lacked continuous prognosis-improving therapy prior to CA. In terms of cluster dynamics, an overall increase in healthcare utilization toward the CA was observed across clusters. In Clusters S, P, and PS, this change occurred mainly in the sixth quarter, marked by a slight shift from the dominant state to states involving cardiologist consultations. However, patients in these clusters experienced relatively stable care throughout the observation period. Conversely, Clusters G and especially Cluster Mix exhibited escalating dynamics starting from the middle of the observa-

tion period. Both clusters showed increases in medication events, with Cluster Mix reaching medication levels comparable to Cluster PS toward the CA. Additionally, Cluster Mix demonstrated a gradual increase in cardiologist involvement over time. The population differed significantly across clusters in terms of patient characteristics. Compared to the other clusters, Cluster Mix was younger, more urban, had the lowest proportion of women, showed less comorbidity, lower mortality after CA, and higher rates of NID and of participation in the DMP for CAD. Cluster S contrasted sharply, with an older, mostly rural population, the highest proportion of women, higher comorbidity scores, the highest mortality rate, and substantially lower use of NID and DMP participation. Clusters P and PS shared similarities with Cluster S regarding age and region but exhibited relatively high rates of DMP enrollment and NID use. Cluster G was similar to Cluster Mix in age, sex, residence, and comorbidity but had significantly lower DMP enrollment and NID use.
We investigated the adjusted correlation of cluster membership and the occurrence of a follow-up CA within 180 days of the first CA using logistic regression. The results revealed that cluster membership was significantly associated with the outcome. Patients in Clusters G, P, S, and PS had significantly higher odds (odds ratios between 1.40 and 1.55; $p<0.05$) of receiving a follow-up CA compared to those in Cluster Mix.

Discussion Comparing the results to treatment guidelines [44], we can see agreement regarding consultations with general practitioners. The overall gradually increasing involvement of cardiologists is also in line with the recommendations. Furthermore, patients in two of the identified clusters experienced treatment that is closer to the guidelines: The younger and more urban population from Cluster Mix, who started at a low level of care, received both classes of medication to a high extent at the end of the observation period. They also show more guideline-reflecting treatment in terms of NID and DMP participation. The stand-out role of Cluster Mix was confirmed by the significantly lower occurrence of the strongly discouraged medical practice of routinely scheduled follow-up CAs. Cluster PS also exhibited recommended treatment patterns, with the main difference from Cluster Mix being that it maintained a high level of care throughout the entire observation period.
In contrast, three of the identified clusters showed signs of care deficits: Patients in

Cluster G and Cluster S lacked the continuous prescription of prognosis-improving medication prior to invasive CA, which is recommended for every CAD patient. Patients of Cluster P lacked continuous prescription of symptom-improving medication, which could indicate a lower presence of symptoms in these patients. However, procedures intended for symptom improvement (percutaneous coronary intervention) were not more frequent in this group. This, in turn, suggests a similar level of symptoms, making treatment gaps or deviations from recommendations likely in this cluster.

Strengths and limitations This study employed SSA on health insurance claims data. As detailed in section 1.2, claims data offer significant strengths, in particular comprehensiveness, large populations and low selection bias. For this study, the comprehensiveness of the dataset allowed us to define a study population that could be reasonably assumed to have comparable CAD morbidity, based on data from one year prior to the observation period.
However, as noted in section 1.2, claims data also have inherent limitations. For instance, in this study, the data do not include information on the reason for general practitioner visits, which means that some visits may have been for non-cardiac issues, potentially leading to an overestimation of care. Additionally, the analysis did not account for other important care events, that are relevant in the treatment and progression of CAD, in particular the use of antiplatelet agents (which are available without prescription at a low cost), laboratory results and lifestyle changes.
Further strengths and limitations related to the methodological approach of SSA are discussed together with those of the second paper in the overarching section 1.7.

1.6 Summary of Paper II: Coxarthrosis medication use patterns before total hip replacement

Background In this study [58], we investigated the care of coxarthrosis patients who had not yet undergone total hip replacement (THR) surgery. Despite the availability of treatment guidelines [59–62], rates in THR surgery exhibit regional variation unrelated to the population's morbidity [11, 47, 48]. Next to the timing and appropriate indication of THR surgery, which is difficult to assess on a population level, also adherence to the recommended stepped approach for prescribing analgesics, and exhaustion of conservative therapy options, in terms of physiotherapy and pain medication, is often questioned and debated [49, 63–65]. Further, the increasing use of opioids [63, 66, 67] raises concerns, especially in the light of the US opioid epidemic [68–70].
The study's objective was to identify, visualize and investigate empirical pain medication use patterns in coxarthrosis patients. Identified care patterns were investigated by analyzing their univariate correlation with patient characteristics, and their correlation with the occurrence of THR. Results were compared with guideline recommendations, namely the appropriate prescribing of mild analgesics, the stepped prescription approach, cautious handling of opioid prescriptions and the exhaustion of pharmacological treatment options prior to surgery.

Data and Methods We used large claims data from two German statutory health insurances covering the years 2012 – 2015 of adult patients who were diagnosed with coxarthrosis in 2012. The study population was set up of two groups: (1) patients who underwent THR surgery between 2013 and 2015 (THR group), and (2) an equal number of randomly selected coxarthrosis patients without THR surgery (noTHR group).
We applied SSA to identify patterns of pain medication use. Pain medication prescription was categorized following the hierarchical categorization of the World Health Organization (WHO) analgesic ladder [71]. We translated the two care events of 'prescription of mild analgesics (WHO stage 1)' and 'prescription of an opioid (WHO stage 2 and 3)' into three hierarchical states (including the null state), where patients who used medication from multiple WHO stages were assigned to the higher

state.

For each patient, we constructed medication use sequences over a 12-month observation period, starting 12 months before THR surgery for the THR group, and a randomly chosen start date between January 2012 and December 2013 for the noTHR group, ensuring no THR surgery occurred at least one year post-observation. Gower's distance was used to calculate state similarities, taking into account the hierarchical nature of states [35, 53]. An optimal matching algorithm was used to determine sequence similarities [31, 35, 72]. We employed partitioning around medoids algorithm to identify clusters of similar medication use sequences [55]. Clusters were visualized, and their univariate correlation with patient characteristics was investigated. To assess the relationship between medication use patterns and the likelihood of receiving THR surgery, we performed logistic regression using cluster membership as a predictor.

Results The study population comprised 19,950 patients diagnosed with coxarthrosis, with half of them in the THR group and the other half in the noTHR group. The majority were female, over 70 years old, and resided in rural areas. Patients in the THR group tended to be younger, had fewer comorbidities, lived more often in urban areas, and received physical therapy more frequently than those in the noTHR group.

Seven distinct clusters of medication use patterns were identified, ranging from 362 to 12,295 patients (average shilouette width = 0.52). The clusters differed in their dominant state(s) and how the states distribution evolved over time: Patients of the biggest *Cluster N* were most of the time in state N, with no prescriptions. *Clusters M-peak4* and *M-peak8* exhibited rising and falling levels of state M (representing the state of mild analgesic use), with peak uses at months 4 and 8, respectively. *Cluster Increase* showed escalating medication levels toward the end of the observation period. In *Cluster M* consistently high use of mild analgesics was observed. *Clusters Medium-O* and *High-O* were characterized by continuous moderate levels and high levels, respectively, of state O (representing the state with opioid prescriptions).

With Cluster N cromprising 61.6% of the study population, and state N also being very present in clusters M-peak4, M-peak8 and Increase, the prescription-free state N is by far the most common state overall. State M was the prominent medication state

in clusters M, M-peak4, M-peak8, and Increase, collectively accounting for 33.7% of the population. Opioid use was concentrated in Clusters Medium-O and High-O, together comprising 4.7% of patients. Medication levels generally increased toward the end of the observation period, especially in Cluster Increase.
Patient characteristics varied notably between clusters. Cluster N had the lowest percentage of women, lowest comorbidity levels, and lower rates of physical therapy and THR. Cluster Increase patients were younger, resided predominantly in urban areas and showed comparatively high rates of physical therapy and THR (74.6%). Cluster M patients showed the second highest THR rate (68.8%) and exhibited similar characteristics as patients from Cluster Increase, but were more likely to reside in less urbanized areas. Clusters M-peak4 and M-peak8 had the highest physical therapy rates and THR rates of 49.1% and 62.3%, respectively. Clusters Medium-O and High-O included the oldest patients with the highest comorbidity, exhibiting lower rates of THR and physical therapy.
Logistic regression analysis revealed that cluster membership was significantly correlated with the occurrence of THR. Patients in Cluster Increase had the highest odds compared to Cluster N patients, followed by Clusters M, M-peak8, and M-peak4.

Discussion In this study, seven different patterns of pain medication could be identified and visualized.
Two of the seven identified patterns, Clusters Increase and M, could be classified as pathways leading to THR, given their high THR rates and elevated odds for THR. Their patterns likely reflected different pain trajectories: disease progression with worsening symptoms in Cluster Increase, and persistent pain in Cluster M. In both clusters, we observed exhaustion of conservative therapy in terms of pain medication prior to surgery as recommended by guidelines [59–62].
The medication patterns observed in Clusters M-peak4 and M-peak8 could reflect acute pain episodes, typical for the intermittent course of coxarthrosis [73]. However, the relatively high THR rates and odds for surgery in these clusters indicated that factors beyond symptom improvement caused the decrease in medication use after the peak and, thus, possible undertreatment with conservative therapy options.
Treatment gaps in pain medication were also represented by Cluster N, which comprised the largest share of the study population. We cannot assume that the absence

of medication prescriptions in this cluster equates to the absence of symptoms, as more than 40% of Cluster N patients eventually underwent THR.
Our findings suggested that conservative therapy in terms of pain medication was not exhausted prior surgery in a large share of the population, in line with concerns raised by other national and international studies [49, 63, 64, 70, 74, 75]. Further, consistent with other German studies [63, 66], our results suggested that opioids were prescribed cautiously and in accordance with a stepped prescription approach.

Strengths and Limitations As in the first paper [36], this analysis used health insurance claims data, which offer significant strengths, as detailed in section 1.2, particularly their comprehensiveness, large population sizes, and low selection bias. In this study, the comprehensiveness of the dataset enabled us to identify patterns over a one-year observation period, use one year of pre-observation data to select patients with a confirmed coxarthrosis diagnosis, and include only patients in the noTHR group who did not undergo total hip replacement (THR) surgery for at least one year post-observation.
However, as noted in section 1.2, claims data also have inherent limitations. The main limitation in this study is the likely underestimation of mild analgesic use, as these medications are available in small doses without a prescription. Nonetheless, patients have a financial incentive to obtain prescriptions to get reimbursed by the insurance. Since claims data often lack clinical data and do not contain information on patient behaviour, the analysis also does not include other important elements of conservative coxarthrosis management, such as weight reduction or exercise.
Further strengths and limitations related to the methodological approach of SSA are addressed in conjunction with those of the first paper in the overarching section 1.7.

1.7 Discussion and outlook: Using SSA to study empirical patient pathways

In the two papers presented in this thesis [36, 58], we successfully applied SSA to two different patient populations. We showed that SSA can be used to define empirical patient pathways as state sequences derived from comprehensive insurance claims data, to extract meaningful and interpretable patterns, to visualize these patterns and to investigate them further. By comparing identified patterns with guideline recommendations, we revealed potential treatment gaps and deviations from treatment guidelines.
The following paragraphs discuss the methodological aspects, strengths and limitations of both papers related to the SSA approach, and outline directions for future research.

1.7.1 Defining states

In sociological life course research, where the SSA methodology originates, states often represent life stages such as employment or retirement. In health service research, states are often defined based on care events that occur within a specified time unit. Researchers translate care events into states in various ways: some use quantiles of the frequency of selected care events [19, 76], while others use the presence or absence of care events to define states [21].
In our study on CAD patients [36], we build on the latter approach, but, for the first time, combine different types of simultaneous or overlapping care events, namely physician visits and mediation prescriptions, in a single analysis. By including different types of care events within a single SSA, we are able to exploit the potential of the SSA method to summarize the treatment of a large patient population in a holistic manner over a considerable time period. This also addresses the interaction of these care events in routine patient care. This approach is however limited to a rather small number of care events per type due to the growing number of resulting states.
In our study on coxarthrosis patients [58], we focus on a single type of care events, namely medication prescriptions. Here, we explored a novel way of defining states by using hierarchical states that reflect the hierarchical categorization of pain medi-

cation from the WHO [71]: Patients with a prescription of both, mild analgesics and opioids, are assigned to the highest state as were patients prescribed opioids alone. This approach resulted in a small number of meaningful states. However, its applicability is limited to contexts where such hierarchical categorization is appropriate. Future research should further explore methods for defining states based on care events, especially with respect to incorporating multiple types of care events. A promising alternative proposed by Vanasse et al. [20] involves defining multiple state sequences for every patient, each reflecting a different care dimension. Sequence similarities are calculated within each dimension, and a pooled distance matrix as the sum of all distance matrices is used for clustering. This approach results in patient clusters that are consistent across dimensions, unlike strictly parallel analyses. We apply this approach in an upcoming SSA study on diabetes care sequences of adolescents (Buehler, Novelli et al. 2025) [77]. Other strategies for managing multidimensional sequences have been proposed in the sociological context [78, 79]. Their applicability to medical and health services care research are yet to explore in the future.

1.7.2 Sequence similarity

The definition of sequence similarity, along with the associated calculation of the dissimilarity matrix used for clustering, represents a crucial step in the SSA process [19, 33, 72].

We used optimal matching to calculate sequence similarity, an approach which is one of the most common approaches in healthcare SSA studies [16]. Hereby, the similarity between two sequences is determined based on the number of transformations - insertions, deletions, or substitutions of states - required to make them identical. The magnitude of these transformations is calculated using predefined costs for each type of operation. While these costs are most often derived using data-driven methods [16], in our studies, we explored alternative ways to define sequence similarity to better reflect the medical realities of patient care. For this purpose, we chose an approach that bases sequence similarity on the similarity of individual states. State similarity, in turn, is not determined through a data-driven process but is instead defined based on the characteristics of the states themselves - that is, based on the

actual care patients receive. To calculate state similarity, we employed Gower's distance [35, 53], using a feature dataset that uniquely identifies the states (for the feature datasets used, see the supplemental material of the papers 2.5, 2.6). These theory-driven state similarities were then used as substitution costs for calculating sequence similarities.
Additionally, we employed a localized optimal matching algorithm [35], which, unlike the standard optimal matching algorithm, allows the integration of theory-driven defined state similarities into the calculation of insertion and deletion costs as well.
With our approach, we respond to criticism raised towards the use of data-driven methods for cost calculation due to the lack of interpretability of resulting similarity measures [80] and their inability to reflect actual state similarities [35]. We ensure that the parameters used are directly tied to the medical reality of patients, thereby ensuring the contextual meaningfulness of sequence similarities.

1.7.3 Sensitivity analyses

In the application of SSA to healthcare data, there is no standardized process to ensure that identified patterns represent genuine structures manifesting in the studied population, rather than random artifacts arising from specific parameter and dataset configurations. Many authors of SSA studies on health data [e.g. 19, 21, 76] neither address the issue of sensitivity analysis nor mention any efforts in that direction [16].
To ensure the robustness of our results, we conducted several sensitivity analyses. These included varying the clustering algorithm, using different distance measures, and comparing solutions for different numbers of medoids, thus different number of clusters. In the study on coxarthrosis patients, we also varied the population by employing bootstrapping techniques [58, see supplemental material]. These sensitivity analyses allowed us to assess the consistency of cluster solutions and confirmed the stability of the final cluster solution presented in our papers.
Future research should establish standardized processes for incorporating sensitivity analyses into SSA studies in healthcare to ensure that identified patterns reflect true care patterns.

1.7.4 Further challenges for future research

Beyond the challenges already mentioned - such as working with multidimensional sequences and establishing standards for sensitivity analyses - there are additional areas of research that hold significant potential for advancing SSA in healthcare studies.

First, exploring the application of SSA to other healthcare databases or to combined datasets, such as medical records, electronic health records, or data from wearable devices, presents an exciting opportunity. While the health insurance claims data used in our studies offer strong advantages, such as low selection bias and comprehensiveness (see 1.2), applying SSA to other types of data could uncover new insights, for example, into patient behavior.

Furthermore, diagnostic information from health insurance claims or clinical data from other databases could be used to define states that reflect actual health rather than received care. This approach would align more closely with the understanding of states in life course research and the original concept of a 'state', and would allow for the study of disease or health trajectories. A particular challenge would be integrating health trajectories with sequences of healthcare events in combined analyses.

Finally, enhancing the predictive and analytical potential of SSA is another crucial area for future research. While SSA has proven to be a powerful tool for descriptive and exploratory analysis, its current use is limited in terms of enabling causal conclusions or predict patient-related outcomes. We showed how integrating additional analyses, such as regression models to analyze the occurrence of follow-up catheterization [36] and the correlation between medication cluster membership and occurrence of total hip replacement surgery [58], can provide deeper insight into the healthcare situation of the population under study and point to potential underlying mechanisms. However, the current study design of SSA does not allow for the investigation of causal relationships.

1.8 Conclusion

In this thesis, we successfully demonstrated how empirical patient pathways can be identified, visualized and investigated in health insurance claims data using SSA. In our study of patients with CAD, we investigated pathways involving medication use and physician visits leading up to invasive CA. In the study of coxarthrosis patients, we explored pathways of pain medication and their correlation with the occurrence of THR. In both cases, we identified and visualized typical pathways as clusters that grouped patients with similar healthcare pathways.

Our findings highlight significant variation in patient characteristics across these clusters, with cluster membership strongly associated with follow-up catheterization in the study of CAD patients, and with THR in the study of coxarthrosis patients. By comparing clusters with treatment guidelines, we could identify clusters in each study that aligned well with guideline recommendations. However, the comparison also revealed potential treatment gaps and deviations from guidelines in substantial parts of the population, especially regarding the exhaustion of conservative therapy options prior moving to revascularization in the case of CAD patients, or THR in the case of coxarthrosis patients. These findings underscore the need for continued health policy efforts to encourage both patients and providers to exhaust conservative therapies before resorting to invasive methods. Additionally, further research is required to investigate the factors driving guideline-deviating behavior on both the supply and patient sides.

Our studies demonstrate how SSA, a method originating in the social sciences, can be effectively applied in healthcare research. We explored different approaches to defining states reflecting healthcare and discussed key methodological aspects of SSA. SSA enables comprehensive, exploratory analyses of large datasets, facilitates the visualization and understanding of healthcare patterns across extensive patient populations, and captures the heterogeneity and diversity of empirical pathways. These abilities make SSA a powerful tool for exploratory healthcare and health services research.

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2 Publications

2.1 List of publications

Paper I

Novelli A., Frank-Tewaag J., Franke S., Weigl M., & Sundmacher L. (2024): Exploring heterogeneity in coxarthrosis medication use patterns before total hip replacement: a State Sequence Analysis. *BMJ Open 14*(9):e080348.

Paper II

Novelli A., Frank-Tewaag J., Bleek J., Günster C., Schneider U., Marschall U., Schlößler K., Donner-Banzhoff N., & Sundmacher L. (2022): Identifying and Investigating Ambulatory Care Sequences Before Invasive Coronary Angiography. *Medical Care 60*(8):602-609.

2.2 Contributions to the publications

I developed the research questions and determined the study designs and overall methodological approaches for both papers. I made the key methodological decisions for the analyses, including the creation of the study populations and specifying details of the SSA. I cleaned and prepared the data for analysis, performed all statistical analyses, and interpreted and discussed the findings. I wrote the manuscripts and, as corresponding author, communicated with the journals.
For Paper II, I was also involved in defining the dataset and coordinating with the health insurance providers who supplied the data.

2.3 Paper I: Ambulatory care sequences before invasive coronary angiography

Title: Identifying and investigating ambulatory care sequences before invasive coronary angiography
Authors: Novelli A., Frank-Tewaag J., Bleek J., Günster C., Schneider U., Marschall U., Schlößler K., Donner-Banzhoff N., Sundmacher L.
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OPEN

Identifying and Investigating Ambulatory Care Sequences Before Invasive Coronary Angiography

Anna Novelli, MA Dott. mag.,† Julia Frank-Tewaag, MSc,† Julian Bleek, Dr. med.,‡ Christian Günster, Dipl.-Math.,§ Udo Schneider, Dr. rer. pol.,‖ Ursula Marschall, Dr. med.,¶ Kathrin Schlößler, Dr. med.,#** Norbert Donner-Banzhoff, Dr. med.,# and Leonie Sundmacher, Dr. rer. oec.**

Background: The concept of care pathways is widely used to provide efficient, timely, and evidence-based medical care. Recently, the investigation of actual empirical patient pathways has gained attention. We demonstrate the usability of State Sequence Analysis (SSA), a data mining approach based on sequence clustering techniques, on comprehensive insurance claims data from Germany to identify empirical ambulatory care sequences. We investigate patients with coronary artery disease before invasive coronary angiography (CA) and compare identified patterns with guideline recommendations. This patient group is of particular interest due to high and regionally varying CA rates.

Methods: Events relevant for the care of coronary artery disease patients, namely physician consultations and medication prescriptions, are identified based on medical guidelines and combined to define states. State sequences are determined for 1.5 years before CA. Sequence similarity is defined for clustering, using optimal matching with theory-informed substitution costs. We visualize clusters, present descriptive statistics, and apply logistic regression to investigate the association of cluster membership with subsequent undesired care events.

Results: Five clusters are identified, the included patients differing with respect to morbidity, urbanity of residential area, and health care utilization. Clusters exhibit significant differences in the timing, structure, and extent of care before CA. When compared with guideline recommendations, 3 clusters show signs of care deficits.

Conclusions: Our analyses demonstrate the potential of SSA for exploratory health care research. We show how SSA can be used on insurance claims data to identify, visualize, and investigate care patterns and their deviations from guideline recommendations.

Key Words: patient pathway analysis, sequence clustering, ambulatory treatment pathways, coronary artery disease, insurance claims data

(*Med Care* 2022;60: 602–609)

The concept of treatment pathways has become a recognized instrument for process optimization, quality assurance, and improved efficiency of care. Pathway-based programs and treatment guidelines are being increasingly applied in the clinical and the outpatient sector to encourage treatment according to current medical evidence and to guide patients through the health system.[1] They are strongly normative in character and aim to provide an "ideal care path." More recently, the investigation of actual, empirical patient paths has gained attention. By analyzing treatment patterns or sequences in comprehensive data, the aim is to obtain a more holistic insight into care processes and to identify possible care deficits or deviations from desired treatment paths. In addition, factors that impact on care and correlations between patterns and health-relevant outcomes are investigated.[2–5] Data mining methods such as pattern mining, clustering, and classification methods are used to identify and investigate patient pathways, hereby exploiting the increasing availability of comprehensive data.[3,5–7] Recently, first efforts have been made to apply a class of sequence clustering methods rooted in sociology and referred to as "State Sequence Analysis" (SSA),[8,9] on health data to identify, visualize, and investigate empirical patient pathways and care utilization patterns.[7,10–12]

In this study, we apply SSA to German health insurance claims to investigate the empirical ambulatory care sequences of

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Data used in the analyses presented in this article are routinely collected insurance claims. Data were pseudonymized and partially reduced to impede reidentification of individuals. Approval for data linkage and data transfer to analysts was asked and granted in advance by the German Federal Social Insurance Authority (Bundesversicherungsamt) under §75 SGB X in case of nationwide statutory health insurances.

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The authors declare no conflict of interest.

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patients with coronary artery disease (CAD) before undergoing invasive coronary angiography (CA) using a left heart catheter. CA allows the visualization of the coronary vasculature and is used in patients with known or suspected CAD, usually in connection with and as a basis for decision-making for revascularization therapy, namely coronary artery bypass graft or percutaneous coronary intervention (PCI).[13,14] This patient group is of particular interest: In Germany, CA rates have increased in recent decades,[15,16] are strikingly high when compared with other countries,[17–21] and show considerable unexplained regional variation.[16,22] This has led to an ongoing discussion as to whether these rates reflect the actual need for CA or whether CA is performed too frequently in patients with stable CAD as a standard diagnostic procedure, or before conservative medical therapy options are exhausted.[16,17,22,23] These deviations from national and international treatment guidelines[13,14,24] may be driven by supply structures, medical uncertainty regarding the indication, patient preferences, and established, regionally prevailing medical practice and treatment paradigms.[16,17,22,23,25]

The aim of the SSA presented in this study is to provide insight into the care process that precedes the CA and to compare it with guideline recommendations, in particular regarding the use of conservative management options. As a methodological contribution, we demonstrate how to jointly analyze care events of different thematic areas that can occur simultaneously, namely physician visits and medication use. For clustering, we advocate the use of a theory-driven approach to determine sequence similarity from a medical and health service perspective. Clusters are visualized and investigated using correlation analyses. In particular, we were interested in routinely performed follow-up CAs, which are strongly discouraged by current guidelines[13,24] and can be seen as a sign of an inappropriate indication,[22,26,27] but may be still prevalent in everyday medical practice.[23,25]

METHODS

Data and Study Population

We conducted a longitudinal cohort study using routinely collected insurance claims data obtained from 3 German health insurances (AOK, BARMER, Techniker Krankenkasse) that share a comprehensive basic reimbursement catalogue and covered ~41% of the German population in 2016.[28,29] The data encompasses all adults undergoing CA in the year 2016, detailing all the patients' reimbursable inpatient, outpatient and prescription claims between 2014 and 2017, diagnoses and basic demographic information. From this data, the study population was defined. All patients who underwent the index event of a CA in July or October 2016 were eligible. The available data allowed to define for each patient an observation period of 1.5 years preceding the CA and a preobservation period of 1 year preceding the observation period (Fig. 1). The restriction to July and October is due to study design reasons (see the Definition of states and sequences section). Based on clinical events recorded during preobservation and observation period, the study population was further restricted to enhance the similarity in regard to CAD morbidity: We included only patients: (1) with known CAD, that is, for whom a diagnosis of stable CAD was recorded in at least 2 quarters within the outpatient sector or at least once within the hospital in the preobservation period; (2) who did not undergo revascularization therapy of any type or CA in the 2.5 years preceding the index CA; and (3) for whom no acute coronary event was registered during the observation period, to account for the considerable difference in clinical state that necessitate diverging treatment recommendations. Only patients, who were continuously insured between 2014 and 2017, or until death during this period, were included.

State Sequence Analysis

The SSA is conducted in 4 steps: (1) choice of care events; (2) definition of states and sequences; (3) definition of (dis-)similarity and clustering; and (4) investigation of clusters. These steps are described as follows. Analyses were performed with R and Stata, including the TraMineR package[9,30] and the comorbidity package.[31]

Relevant Care Events

Four care events, that are reliably traceable in claims data, were chosen for consideration in the sequences:

- G: consultation of a **g**eneral practitioner.
- C: consultation of an office-based **c**ardiologist.
- P: prescription of **p**rognosis-improving medication.
- S: prescription of **s**ymptomatic medication.

This selection was based on the national treatment guideline for stable CAD,[13] on analyses of national and international guidelines,[32] and on medical expert opinion. Prognosis-improving medication, which is recommended for every patient due to its effect on CAD morbidity and mortality,[13,14] includes all lipid modifying agents licensed in Germany. Symptom-oriented medication, which is to be applied depending on symptom level and comorbidities of the patient, covers beta-blockers, calcium channel blockers, ivabradine, ranolazine, and organic nitrates.[32] Other clinical data points, such as the medication of antiplatelet agents (obtainable without prescription), laboratory results, and lifestyle changes were not considered since these are not covered by claims data.

We derived the physician's specialty based on specialty-specific billing codes. Patients with a relevant prescription issued by a physician, whose specialty group could not be determined or was not included in the analysis, were excluded (217 patients).

Definition of States and Sequences

First, the time unit and duration of sequences, determining the observation time, were defined. Due to quarterly-based remuneration schemes in the German outpatient sector, care events as "physician consultations" can only be determined reliably within a yearly quarter. Thus, a quarter of a year is the smallest possible time unit and was used for this analysis. For each patient, the sequence period was defined as the 6 quarters before the index CA. The quarter in which the CA took place is itself not part of the observation period (Fig. 1). This necessitated the restriction to patients with the CA in the first month of a quarter (July or October 2016) to minimize the unobserved time between the end of the sequence and the index CA.

States are specified as combinations of the 4 chosen care events. Thirteen states were included, N, G, C, GC, GP,

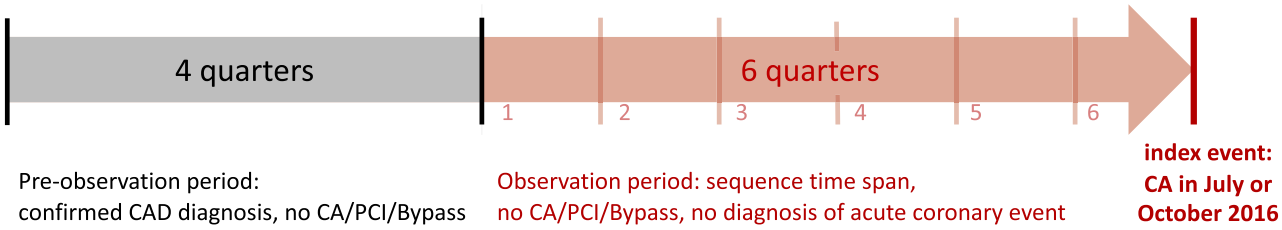

FIGURE 1. Visualization of preobservation and observation period preceding the index CA. CA indicates coronary angiography; CAD, coronary artery disease; PCI, percutaneous coronary intervention.

CP, GCP, GS, CS, GCS, GSP, CSP, GCSP with state "N" denoting the state in which no care events were recorded. For each patient and each quarter of the observation period, the patient's state was determined by examining which of the state-defining care events had been recorded. Thus, each patient's state sequence consisted of 6 consecutive states.

Definition of Dissimilarity and Clustering

A crucial step in clustering is the choice of a (dis-) similarity measure defining when 2 objects, or sequences, are considered similar or, conversely, dissimilar.[30,33] We applied a localized optimal matching approach to determine sequence dissimilarity.[30,34] Within this approach, we used Gower distance to assure that state similarity and, consequently, sequence similarity reflects the similarity of care from a health services and medical perspective.[30,35] For clustering, we used a partitioning around medoids algorithm and performed clustering for different numbers of initial medoids (between 3 and 10), thus different numbers of clusters.[36] The optimal number of clusters was determined using the weighted average silhouette width.[37] Further details are described in the Supplemental Material (Supplemental Digital Content 1, http://links.lww.com/MLR/C467).

Statistical Investigation of Clusters

Clusters were visualized using frequency plots and distribution plots. We calculated summary statistics and performed χ^2 tests to investigate clusters and their unadjusted correlation with patient characteristics.

Analysis of Re-catheterization

We used logistic regression to study the discouraged medical practice of re-catheterization (CA) for controlling purposes only. We included membership to previously identified clusters as a patient characteristic into the regression model. We defined re-CA as a second invasive CA within 180 days of the index CA. To identify routinely scheduled re-CAs, we excluded patients for whom an acute coronary event was recorded concurrently with the re-CA and disregarded CAs performed in the context of the index CA (recorded within 30 d of the index CA or in the same billing case as the index CA). Patients who died within the 180-day period were excluded.

The covariables used in the regression were cluster membership, patient characteristics (age, sex),[38,39] comorbidity indices (van Walraven-Elixhauser score),[40,41] regional characteristics (degree of urbanization, residence in East/West Germany),[42] variables reflecting health services utilization [enrollment in the CAD Disease Management Program (DMP), use of noninvasive diagnostics (NID)] and variables characterizing the circumstances of the index CA (PCI, bypass, acute coronary event).[16,17,22,26,43] Further details are provided in the Supplemental Material (Supplemental Digital Content 1, http://links.lww.com/MLR/C467). Regression results are reported with odds ratios and their 95% confidence intervals. A *P*-value of $P < 0.05$ was regarded as statistically significant.

RESULTS

Cluster Analysis

The study population consists of 11,535 patients. Patient characteristics are shown in Table 1.

Cluster Identification

Five clusters were identified (weighted average silhouette width = 0.35), with their size varying between 963 and 4145 patients. Figure 2 shows for each cluster the 10 most frequent sequences, the quarterly distribution of states and of events.

Each cluster is dominated by 1 or 2 states. Cluster 1 is dominated by State G (hereinafter termed "cluster G"), cluster 2 by states G and GPS ("cluster Mix"), cluster 3 by state GP ("cluster P"), cluster 4 by state GS ("cluster S"), and cluster 5 by the states GPS and GCPS ("cluster PS").

Physician Consultations. The strong role of the general practitioner is clearly visible: Each of the cluster-dominating states includes event G. Overall rates of cardiologist involvement are comparatively low and states with event C without G are negligible. The lowest and highest cardiologist participation can be observed in cluster G and cluster Mix, respectively.

Medication Events. Cluster-dominating states differ by medication events. In clusters Mix and PS (19.9% of the study population), most patients received medication from both classes in the last 2 quarters before CA. In clusters G and S (44.2% of the study population) the absence of continuous prognosis-improving therapy before CA can be observed for most patients.

Cluster Dynamics. Across clusters, an increase in health care use towards the CA is visible. In clusters S, P, and PS, this change occurs mainly in the sixth quarter by means of a shift from the dominant state to the corresponding state with cardiologist involvement. However, this dynamic is moderate, and many patients experience a rather stable care situation throughout the observation period in these 3 clusters.

TABLE 1. Unadjusted Summary Statistics by Sequence Clusters

Patient Characteristics	Total	G	Mix	P	S	PS	*P*
No. patients	11,535	2261	1334	963	2832	4145	
% of study population		19.6	11.6	8.3	24.6	35.9	
Age (% of patients) (y)							
< 69	23.7	27.3	30.7	24.3	18.4	22.8	< 0.001
69–76	28.5	27.5	31.4	28.4	24.5	30.8	
77–80	21.8	20.7	19.5	22.4	22.7	22.4	
> 80	26.1	24.4	18.4	24.9	34.4	24.0	
Women	37.0	33.5	25.9	30.1	47.3	37.1	< 0.001
Living area (% of patients)							
Major city	25.8	27.8	29.2	25.3	24.0	25.0	< 0.001
Urban area	34.9	37.6	40.9	35.9	30.6	34.1	
Rural area, densely populated	19.1	16.6	16.0	19.4	20.9	20.1	
Rural area, sparsely populated	20.3	18.0	13.9	19.3	24.5	20.8	
Region: patients living in East Germany	25.8	23.2	22.3	23.1	31.1	25.2	< 0.001
Patients with an acute coronary event within CA billing case	24.1	24.4	23.2	24.5	25.1	23.4	0.435
Elixhauser Comorbidity Score							
Based on ambulatory diagnoses							
Mean (SD)	10.8 (9.3)	9.4 (9.2)	10.2 (9.3)	10.3 (9.1)	11.5 (9.4)	11.3 (9.3)	< 0.001
Based on hospital diagnoses							
Mean (SD)	10.0 (9.3)	9.0 (9.0)	8.8 (9.1)	8.6 (9.2)	11.5 (9.5)	10.2 (9.3)	< 0.001
Patients enrolled in DMP	48.3	35.6	53.5	54.2	41.9	56.5	< 0.001
Patients with noninvasive diagnostics within 3 mo before CA	33.8	33.4	41.9	35.7	28.9	34.3	< 0.001
Patients receiving invasive procedure following CA within 30 d after index CA or within same billing case							
PCI	38.6	38.6	39.9	38.3	40.3	37.0	0.067
CABG	4.8	5.1	5.3	4.2	4.4	4.8	0.534
Patients with re-CA within 30–180 d after index CA*	6.4	6.7	5.2	6.8	6.0	6.8	0.296
Patients who died within 180 d after index CA	8.6	7.5	5.6	7.2	11.6	8.3	< 0.001

*For the re-CA rate, the denominator population is not the entire study population of 11,535 patients, but only 10,427 patients, since 986 patients were excluded since they died in the timeframe of 180 days and 122 patients were excluded because an acute coronary event was coded in the billing episode of the second CA.

CA indicates (invasive) coronary angiography; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; DMP, structured disease management program for coronary artery disease patients; PCI, percutaneous coronary intervention; re-CA, re-catheterization.

In contrast, cluster G and, to a considerably greater extent, cluster Mix exhibit escalating dynamics from the middle of the observation period on. Both clusters show an increase in medication events. While the increase in cluster G is small, cluster Mix reaches medication levels as high as those of cluster PS towards the CA. In addition, cluster Mix shows a gradual increase of cardiologist involvement throughout the observation period.

Patient Characteristics by Sequence Clusters

Patient characteristics differ significantly between clusters (Table 1).

Cluster Mix has the youngest, mostly urban population and the lowest percentage of women. Its patients seem to be healthier in general, with a low comorbidity index and the lowest 180-day mortality rate. Additional indicators of health care use, NID use and DMP participation, are by far the highest, respectively above average in this cluster.

Cluster S provides the greatest contrast to cluster Mix. It is characterized by a significantly older, mostly rural population, with more comorbidities, the highest mortality rate and the highest proportion of women. NID use and DMP participation were substantially lower than in other clusters.

While clusters P and PS show similarities to cluster S in terms of age distribution and the region of residence, relatively high rates of DMP enrollment and NID use can be observed.

Finally, cluster G is comparable to cluster Mix in terms of age, sex, residential area and comorbidity, but shows significantly lower rates of DMP enrollment and NID use.

Neither the occurrence of an acute coronary event, nor subsequent re-CA within 180 days, nor bypass surgery within 30 days of the CA show associations with cluster membership in unadjusted correlation analysis. A slight tendency for correlation ($P = 0.07$) might be present for PCI within 30 days of CA.

Occurrence of Re-catheterization

The identified clusters were included as a predictor in a logistic regression model, with the occurrence of a second CA within 180 days (re-CA) of the index CA as dependent variable. The patient population for the regression was reduced to 10,427 patients, excluding 986 patients who died in the relevant period and 122 patients for whom an acute coronary event was diagnosed within the billing episode of the second CA. Regression results are presented in Table 2.

Across clusters, 6.4% of patients experienced a re-CA. The logistic regression reveals that by adjusting for patient characteristics and morbidity, cluster membership is significantly associated with re-CA: Patients of clusters G, P, S, and PS have higher odds compared with those of cluster Mix. Older patients show decreased odds for a re-CA. Being female is negatively associated with receiving re-CA. Significantly increased odds for re-CA are seen in patients who live in former East Germany. Eight-fold odds are seen in patients who received a PCI within 30 days of the index CA.

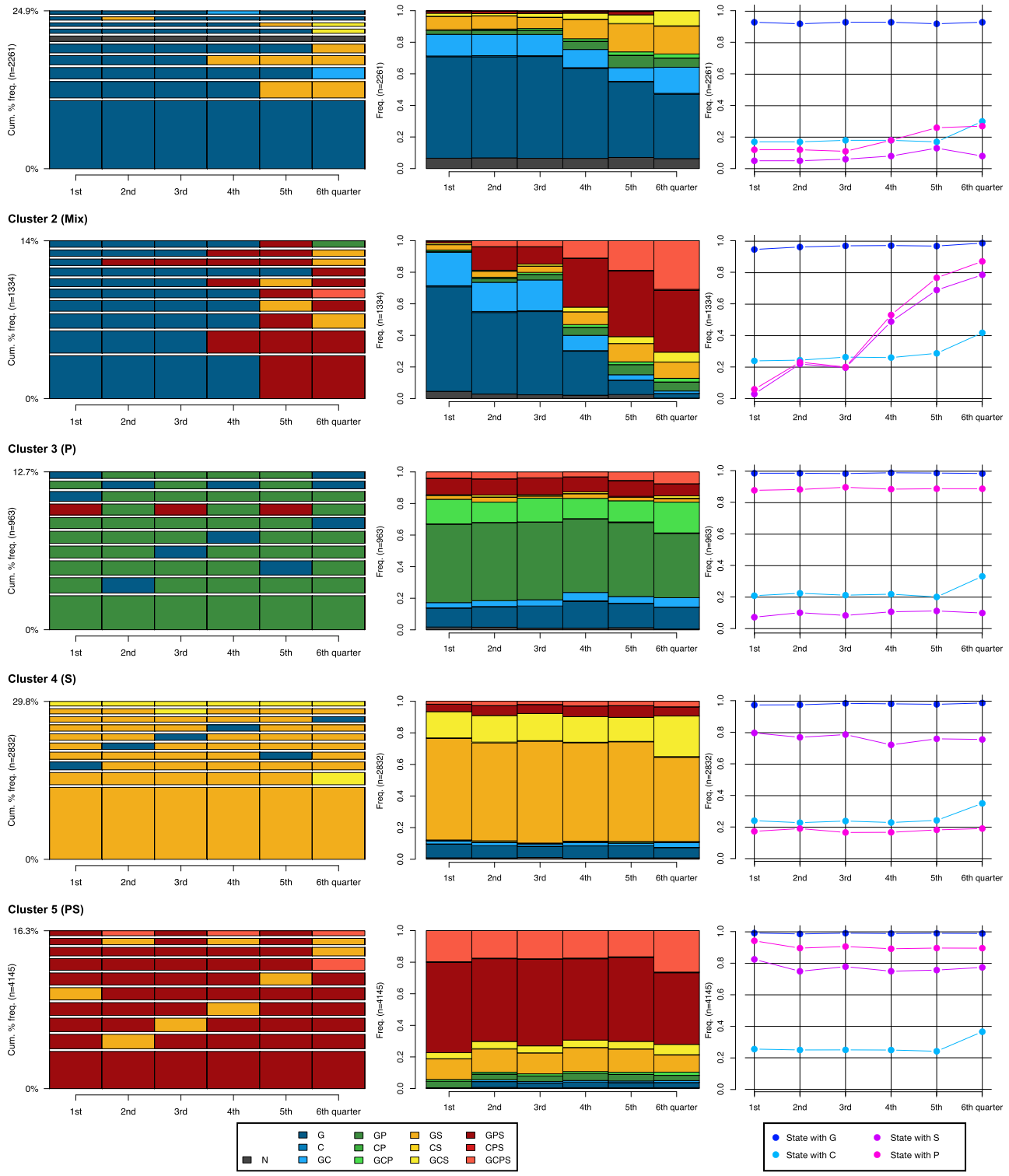

FIGURE 2. Frequency (left) and distribution plots (middle and right) for each of the 5 identified clusters. The frequency plots show the 10 most frequent sequences of each cluster. The *y*-axis shows cumulative frequency; thus, the height of the sequences is relative to their occurrence. The distribution plot in the middle show the distribution of states in each quarter of the observation period. The 13 states in the figures on the left and in the middle are color-coded, with the ground color (blue/green/yellow/red) used to indicate the combination of medication events (none/P/S/PS) and the brightness (dark/middle/bright) used to indicate the accompanying physician events (G/C/GC). The distribution plot on the right-hand side visualizes the event distribution throughout the observation period.

TABLE 2. Results of Logistic Regression for Re-catheterization Within 180 Days After the Index CA

Independent Variables	OR	*P*	95% CI
Reference: cluster Mix			
Cluster G	1.48	0.015	1.08; 2.03
Cluster P	1.51	0.031	1.04; 2.21
Cluster S	1.40	0.035	1.02; 1.92
Cluster PS	1.55	0.003	1.16; 2.07
Reference: age < 69 (y)			
69–76	0.79	0.036	0.64; 0.98
77–80	0.82	0.104	0.65; 1.04
> 80	0.54	< 0.001	0.42; 0.70
Reference: male			
Female	0.70	< 0.001	0.58; 0.85
Living area, reference: major city			
Urban area	1.18	0.150	0.94; 1.46
Rural, densely populated	0.93	0.576	0.73; 1.19
Rural, sparsely populated	0.98	0.871	0.76; 1.25
Region, reference: West Germany			
East Germany	1.37	0.002	1.12; 1.68
Elixhauser Comorbidity Score			
Ambulatory	1.00	0.561	0.99; 1.01
Hospital	1.00	0.431	0.99; 1.01
Revascularization procedure within 30 d, reference: none			
PCI	8.56	< 0.001	6.92; 10.59
CABG	0.50	0.132	0.20; 1.23
Acute coronary event in billing case of index CA	1.01	0.929	0.84; 1.21
NID within 3 mo before CA	1.13	0.190	0.94; 1.35
DMP	1.01	0.934	0.85; 1.19
Constant	0.02	< 0.001	0.01; 0.02

CA indicates (invasive) coronary angiography; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CI, confidence interval; DMP, structured disease management program for coronary artery disease patients; NID, noninvasive diagnostic procedure; OR, odds ratio; PCI, percutaneous coronary intervention.

DISCUSSION

In this study, we apply SSA to comprehensive insurance claims data from 3 German health insurances to explore ambulatory care patterns of patients with CAD before undergoing CA. Due to the high number of observations and since the data cover multiple years, it was possible to create a study population that is approximately homogeneous in terms of CAD morbidity, despite the absence of clinical or lifestyle information.

Identified Treatment Patterns

For patients with stable CAD, our analysis demonstrates the heterogeneity of treatment patterns preceding CA with respect to physician consultations and medication. We identified and visualized 5 clusters of care sequences.

In all clusters, the majority of patients consulted general practitioners throughout the observation period. This is consistent with guideline recommendations that emphasize the responsibility of general practitioners to coordinate continuous evidence-based care.[13] Although overall cardiologist involvement is relatively low, an increase is visible towards the index CA as recommended in the guidelines.[13]

Clusters differ with respect to the medication prescribed, the extent of cardiologist participation, and the development over time.

Two clusters, clusters Mix and PS, show a high intensity of care before CA, alongside high rates of DMP enrollment and NID. While the older and more comorbid population of cluster PS received this level of care continuously, the younger, urban and healthier patients of cluster Mix evolve to reach this high level of care. Its patients experience treatment closely reflecting the guidelines, with optimal medication therapy, cardiologist involvement, DMP enrollment and NID use. This could be guided by the physician, by the behavior of informed patients, or by supply structures in urban areas.

The remaining 3 clusters lack the presence of 1 or both medication events: A substantial proportion of clusters P and G does not receive continuous symptom-improving medication. One might hypothesize that this absence of medication reflects the absence of symptoms. This would imply that CA was not performed out of symptomatic, but out of prognostic indication. However, the absence of higher coronary artery bypass graft rates in these clusters does not support this hypothesis. In another scenario, patients might undergo CA considering revascularization out of symptomatic indication. In this case, contrary to guideline recommendations, revascularization therapy seems to have been considered before conservative symptomatic drug therapy options had been exhausted.

Patients from clusters G and S do not receive continuous prognosis-improving medication, even immediately preceding CA. This indicates deficits in the care of stable CAD patients and a deviation from guideline recommendations. Notably, cluster S has the highest proportion of female patients. This reminisces the repeatedly stated hypothesis of underestimation and undertreatment of CAD in women.[38,39,44–46]

To gain additional insight, a logistic regression was performed with re-CA within 180 days as the outcome. The observed re-CA rate of 6.4% is substantial, yet significantly lower than in a previous study,[25] most likely due to our conservative approach in the operationalization of re-CA.

The regression revealed that older and more comorbid patients are less likely to receive a re-CA. This meets our expectations since providers might refrain from routinely scheduling of re-CAs for patients with higher procedural risks. A similar reasoning was hypothesized by Piedmont et al[22] in a comparable context. Our results on the correlation between PCI at index event and re-CA also complement the descriptive results of Jeschke et al.[25] With respect to cluster membership, we find that patients of cluster Mix have lower odds for re-CA compared with all other clusters. This confirms the characterization of cluster Mix as being in good accordance with guidelines. A possible explanation could be that for patients from this cluster, being the youngest and healthiest, a second intervention, even only for controlling purposes, seems unnecessary. Another probable scenario is that these patients or their physicians refrain to a higher degree from performing re-CA in general.

Strengths and Limitations

This is the first SSA on insurance claims data that includes different kinds of simultaneous or overlapping care events, namely physician visits and medication, in a single analysis. Previous studies have focused on the frequency or volume of health service utilization alone, or on different care events in separate analysis.[7,10–12] Our combined approach enables to exploit the potential of the SSA method to capture

the treatment of large patient population in a holistic manner over a considerable period. The method is however limited to a rather small number of care events per type (due to the growing number of resulting states). This also implies that health care can be captured only with respect to the selected events. We identified 5 clusters. The silhouette coefficient, which reflects intracluster homogeneity and intercluster heterogeneity, is 0.35. Comparing to previous studies,[7,10,11] this value indicates a high level of cluster quality, in particular since our combined approach is done at the expense of a larger number of states with a corresponding increase in sequence heterogeneity. We advocate the use of a theory-driven definition of state and consequently sequence dissimilarity. This allows to capture the medical relevance of a transition between 2 states, which is not guaranteed for standard data-driven dissimilarity measures.

From a health care management perspective, our results provide health policymakers and care providers with easily accessible and comprehensive insights into the health care situation of CAD patients in Germany. The identified deviations from guidelines may indicate aims of targeted interventions.

Since the study population consists of patients with diagnosed stable CAD, the study results only relate to stable CAD patients. Despite their comprehensiveness, insurance claims data have some limitations. The reasons for physician consultations are not reported and could also be noncardiac issues. Since physicians in Germany receive remuneration partly in quarterly flat rates, physician visits can only be determined on a quarterly basis, and the frequency of visits per quarter cannot be reliably determined. Further, the data do not contain clinical or lifestyle information. Thus, it is not possible to determine whether the indication for CA reflects morbidity-based need or observed deviations from guideline care do indicate suboptimal therapy. For example, a fast progression of symptoms may necessitate early revascularization. However, it can be reasonably assumed that such phenomena occur at a much smaller scale than the macrolevel picture enabled by SSA. For instance, our analysis revealed that 2 clusters, constituting substantial 44% of the study population, do not receive continuing prognosis-improving medication before CA.

CONCLUSIONS

This study investigated ambulatory care sequences preceding invasive CA among patients with stable CAD. To this end, we applied sequence clustering techniques on German health insurance claims. Different types of care events were considered within a combined SSA. Based on a theory-driven approach to determine sequence similarities, 5 clusters of treatment patterns were identified. Alongside CAD morbidity and comorbidity, regional structures, patient preferences, or medical practice patterns might influence treatment pathways. The comparison to guideline recommendations suggests the presence of care deficits within some clusters and may indicate starting points of further research and targeted interventions. Logistic regression revealed that cluster membership is correlated with the risk of subsequent health interventions. Future studies should further explore the potential of SSA for patient phenotyping, risk stratification, and predictive modeling of health outcomes and health care use.

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2.4 Paper II: Coxarthrosis medication use patterns before total hip replacement

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

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ABSTRACT

Objective Evidence of geographical variation in total hip replacement (THR) and deviations from treatment guidelines persists. In this exploratory study, we aim to gain an in-depth understanding of patients' healthcare trajectories by identifying and visualising medication use patterns in coxarthrosis patients before surgery. We examine their association with patient characteristics and THR, and compare them with recommendations on mild analgesics, opioid prescription and exhaustion of conservative therapy.

Methods In this exploratory study, we apply State Sequence Analysis (SSA) on German health insurance data (2012–2015). We analyse a cohort of coxarthrosis patients, half of whom underwent THR after a 1 year observation period and half of whom did not undergo surgery until at least 1 year after the observation period. Hierarchical states are defined based on prescriptions. We construct sequences, calculate sequence similarity using optimal matching and identify medication use patterns via clustering. Patterns are visualised, descriptive statistics are presented and logistic regression is employed to investigate the association of medication patterns with subsequent THR.

Results Seven distinct medication use patterns are identified, correlating strongly with patient characteristics and subsequent THR. Two patterns leading to THR demonstrate exhaustion of pharmacological therapy. Opioid use is concentrated in two small patterns with low odds for THR. The most frequent pattern lacks significant pharmacological therapy.

Conclusions This SSA uncovers heterogeneity in medication use patterns before surgery in coxarthrosis patients. Cautious opioid handling and adherence to a stepped prescription approach are observed, but many patients display low medication therapy usage and lack evidence of exhausting conservative options before surgery.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study employs innovative sequence clustering methods to identify, visualise and investigate medication patterns among patients with coxarthrosis.
⇒ Correlation analyses with patient characteristics and logistic regression modelling, with the occurrence of total hip replacement as the outcome, are used to characterise and comprehend the identified patterns.
⇒ The analysis is based on a large dataset from German health insurance records spanning multiple years.
⇒ This study examines prescription medications only.

INTRODUCTION

Numerous evidence-based guidelines exist for the treatment of coxarthrosis, that aims to reduce pain, slow joint degeneration and maintain or restore joint functionality and mobility.[1–8] Despite their availability, significant regional variations in total hip replacement (THR) rates have been observed in Germany[9] and internationally,[10–12] which cannot be fully accounted for by morbidity differences in the population. Studies have identified and discussed various non-morbidity-related factors, including supply structures, regional differences in medical practice paradigms, physician preferences, as well as social and economic factors.[9 11 12] These factors can influence treatment decisions for coxarthrosis patients and may lead to deviations from guidelines.

Many studies have investigated healthcare utilisation among coxarthrosis patients, focusing on the appropriate use of conservative therapy options, potential opioid misuse, and the appropriateness and timeliness of THR indications. Several German and international studies have reported potential underutilisation of conservative therapy options, especially physiotherapy and medications from step 1 of the WHO analgesic ladder (including non-opioid analgesics, non-steroidal anti-inflammatory drugs (NSAID) and cyclo-oxygenase-2 inhibitors, hereinafter referred to as 'mild analgesics').[13–18] Some studies have criticised deviations from the stepped prescription approach,[15 16] although positive evidence for its application exists.[19]

Another concern pertains to the potential misuse or overuse of opioids (steps 2 and 3 of

the WHO analgesic ladder[13]), particularly in light of the US opioid epidemic.[20–22] While the extent of opioid use in Germany is not considered epidemic, researchers have noted the rising number of opioid prescriptions overall and among osteoarthritis patients.[14 19 23] Furthermore, the observed geographical variation in THR rates[9–12] raises questions about the appropriateness and timeliness of the decision for THR surgery. Although assessing the appropriateness of indications for THR at the population level remains challenging, one study compared healthcare utilisation of patients prior to surgery with the recommendation to exhaust conservative therapy options before undergoing surgery, suggesting that many patients do not receive conservative treatments before undergoing THR surgery.[24]

The majority of these studies and treatment guidelines possess a predominantly normative character. They focus on how patients' care *should* be provided and how their care pathways *should* be designed. However, in recent years, there has been a growing interest in empirical, exploratory patient pathway analyses, that focus on how patients *actually* receive care and navigate the healthcare system.[25] These analyses aim to offer a comprehensive view of the care situation for the patient population under investigation and allow for the identification of characteristic care patterns.[26–28] By comparing these observed, real-world patterns with ideal, normative pathways or guideline-based treatment recommendations, gaps in care and deviations from desired care pathways can be identified.[26 29 30] Analysing the correlation between identified patterns and patient characteristics, supply-side factors or health outcomes can enhance our understanding of healthcare in the studied patient population, explain unexpected patterns or deviations from guidelines, and pinpoint areas for further research.[26 27 29–31]

Various methods, often drawn from the field of data mining, are employed for this purpose.[25] In recent years, a combination of sequencing and clustering methods called 'State Sequence Analysis' (SSA), originally from the social sciences,[32 33] has been successfully applied to healthcare data or health insurance claims data to identify healthcare utilisation patterns of patients.[26 27 29 30] SSA enables the identification, investigation and holistic visualisation of characteristic healthcare patterns.[26 27 29 30]

This study aims to offer insights into the care of coxarthrosis patients who have not yet undergone THR surgery. Our objective is to identify, visualise and investigate empirical pain medication use patterns in these patients, while also examining whether specific medication patterns lead to THR. We will interpret our findings on care patterns in relation to patient characteristics and compare them to guideline recommendations. Key aspects of interest include appropriate prescribing of mild analgesics, the stepped prescription approach, cautious handling of opioid prescriptions and the exhaustion of pharmacological treatment options prior to surgery. To achieve these goals, we will employ innovative sequencing and clustering techniques known as SSA on comprehensive health insurance claims data, use descriptive statistics and apply logistic regression.

METHODS

Data, sample and observation period

Our analysis used comprehensive data from two German statutory health insurers, the Allgemeine Ortskrankenkasse Bayern, which operates in Bavaria, and the Siemens Betriebskrankenkasse, a nationwide operating insurance. The choice of either of these health insurances, beyond geographical limitation, is a free choice of the insured individuals. There are no differences in the services and reimbursements provided by these insurers with respect to the care events analysed in this study. The data, spanning 2012–2015, includes reimbursable claims entailing prescription, diagnoses and demographics for individuals aged 18+ diagnosed with coxarthrosis in 2012. The prescription dataset includes all prescribed and dispensed medications, their quantities, Anatomical Therapeutic Chemical (ATC) classifications and daily defined doses. Only patients with complete demographic information were used for the analysis. We formed an analytical sample comprising two groups, excluding patients with femur fractures, femoral osteonecrosis or complications from orthopaedic devices. The first group consisted of patients with confirmed coxarthrosis who underwent THR surgery between 2013 and 2015 but not in 2012 (THR group). The second group included an equal number of randomly selected coxarthrosis patients without THR surgery between 2012 and 2015 (noTHR group). A coxarthrosis diagnosis was considered confirmed if diagnosed twice in different quarters within the outpatient sector or once in the inpatient sector in 2012. For ICD and procedure codes, see online supplemental material. The observation period (see figure 1) for the THR group was set to 12 months before the month of THR surgery. For the noTHR group, the 12-month observation period start was randomly chosen between 1 January 2012 and 31 December 2013, ensuring that patients did not undergo THR surgery for at least 1 year postobservation.

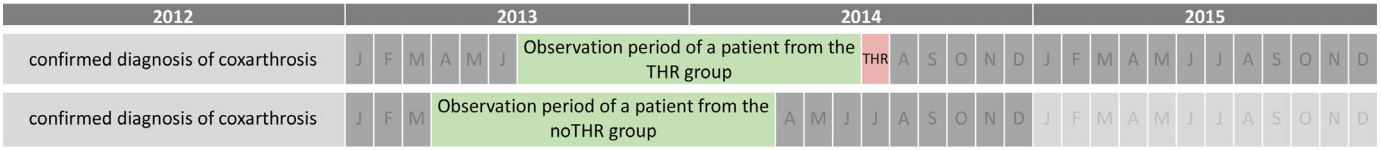

Figure 1 Visualization of the timeline. An exemplary observation period of a patient from the THR and noTHR group is shown. THR indicates total hip replacement; J to D, months.

Definition of medication use sequences

We aimed to identify patterns of pain medication use. An individual patient's medication use sequence is constructed by consecutive states, with each state defined by the prescription events a patient encounters within a specified timeframe. Since medication prescriptions are accurately recorded in German health insurance claims, we used the small time unit of months. Consequently, the 12-month observation period corresponds to sequences of 12 successive states in SSA terminology.

Since the pain management approach for osteoarthritis can also be aligned with the established stage framework of the WHO analgesic ladder,[3 13] we have structured the pharmacological interventions according to the classification outlined in this scheme. We identified prescribed medications based on ATC codes (refer to online supplemental material for ATC codes used) and calculated the days covered by the prescription based on the daily defined dose. A patient was considered a user of the respective medication in a given month if the prescription covered ten or more days. Medication therapies were grouped into three states: 'N' for *n*o prescription, 'M' for *m*ild analgesics (step 1 of the WHO ladder), and 'O' for *o*pioids (steps 2 or 3 of the WHO ladder). It is important to note that small doses of mild analgesics are available over the counter in Germany, which could lead to underestimating their use. States were designed hierarchically, classifying patients based on the highest stage medication if they used medications from multiple stages.

Cluster analysis

To determine medication use patterns, we clustered the defined sequences into groups of similar sequences. This necessitates defining when two sequences are similar or, conversely, dissimilar. We used optimal matching to calculate sequence dissimilarity[32 34 35] employing a feature dataset that reflects the hierarchical nature of the defined states.[35 36] We used partitioning around medoids clustering to group sequences into clusters.[37] To identify the optimal number of clusters, we evaluated quality measures and cluster cut-off criteria for 2–15 clusters, including the Average Silhouette Width (ASW) which reflects intercluster heterogeneity and intracluster homogeneity.[38 39] To choose between solutions with comparable levels of cluster quality, we assessed each cluster solution based on its content validity, cluster size and whether an increased cluster solution contributed an additional cluster with theoretical significance. Based on these factors, we selected the 7-cluster solution. For more information on the cluster analysis, refer to online supplemental material.

In sensitivity analyses, we redraw randomly the noTHR group, conducted analyses with a bootstrapped THR group, and compared the 7-cluster solution to solutions of different orders with comparable quality criteria.

Clusters were visualised using frequency and distribution plots. We calculated summary statistics and performed χ^2 tests to examine clusters and their unadjusted correlation with patient characteristics.

Investigating the relationship between medication use patterns and THR

To investigate the correlation between identified medication use patterns and the likelihood of receiving THR, we employed logistic regression with cluster membership as a categorical predictor variable. Additional independent variables included sociodemographic patient characteristics (age, gender, residential area), Elixhauser comorbidity score for general comorbidity adjustment[40 41] and separate adjustment for opioid dependence. We used a hierarchical, categorical variable for pain based on ICD codes, following the approach of Freytag *et al*[42] with minor modifications (see online supplemental material) to operationalise pain based on ICD diagnoses. We adjusted for the presence of diagnoses in pain categories above the osteoarthritis pain category (cancer, back pain, disc prolapse). Finally, we included a binary variable for physical therapy use. We used directed acyclic graphs to inform the theoretical model for logistic regression,[43] with source code and visualisation available in online supplemental material.

Software used

Analyses were performed using R[44] and Stata.[45] Packages employed include the TraMineR,[33 35] Weighted Cluster[38] and co-morbidity package.[46]

RESULTS

We identified 9975 patients with THR, resulting in a total study population of 19 950 individuals. Patient characteristics for the entire sample, as well as for the THR and noTHR groups, are presented in table 1. The majority of the study population is female, resides in rural regions, and is over 70 years old. By design, 50% of the study population undergoes THR, while less than half of the patients receive physical therapy during the observation period. Patients of the THR group tend to be younger and have fewer comorbidities, reside more frequently in cities and receive physical therapy to a greater extent.

Cluster identification and visualisation

We identified seven clusters (ASW=0.52), ranging in size from 362 to 12 295 patients. Figure 2 displays the 10 most frequent sequences and the monthly distribution of states for each cluster.

The visualisation of clusters in figure 2, shows, that each cluster is dominated by one or two states, with clusters differing in their dominant state(s) and observed dynamics over time. To simplify the presentation and discussion of results, clusters are henceforth referred to as 'cluster N' (state N dominant), 'cluster M-peak4' (rising and falling levels of M, peak in month 4 of the observation period), 'cluster M-peak8' (rising and falling levels of M, peak in month 8), 'cluster Increase' (escalating medication levels towards the end of the observation period), 'cluster M' (consistently high levels of M),

Table 1 Unadjusted summary statistics for the entire sample and for THR and noTHR group

	Total	THR group	noTHR group	P value
Patients (n, %)	19950 (100.00)	9975 (50.00)	9975 (50.00)	
Patients (%) aged				
Below 60 years	20.83	22.88	18.79	
60–69 years	25.81	27.45	24.18	
70–79 years	36.57	37.59	35.54	
80 years and older	16.79	12.08	21.49	<0.0001
Mean age (95% CI)	68.84 (68.69, 69.00)	67.73 (67.52, 67.94)	69.96 (69.73, 70.18)	<0.0001
Women (%)	58.03	58.36	57.69	0.344
Patients living in (%)				
Urban region	27.37	30.36	24.38	
Region with moderate urbanisation	22.10	22.29	21.90	
Rural region	50.54	47.36	53.71	<0.0001
Mean Elixhauser comorbidity score (95% CI)	1.07 (1.02, 1.13)	0.90 (0.83, 0.97)	1.24 (1.16, 1.33)	<0.0001
Patients in the following pain category (%)				
Cancer	3.79	3.49	4.10	0.024
Back pain	33.00	32.87	33.12	0.707
Disc prolapse	13.02	13.24	12.80	0.355
Patients with vertigo (%)	14.48	12.33	16.63	<0.0001
Patients with opioid dependence (%)	0.14	0.15	0.13	0.705
Patients receiving physical therapy (%)	45.97	52.73	39.22	<0.0001
Patients undergoing total hip replacement (%)	50.00	100.00	0.00	

P value comparing patients from THR group and noTHR group using appropriate correlation tests (Pearson's χ^2, Mann-Whitney, t-test).
CI, confidence interval; THR, total hip replacement.

'cluster Medium-O' (continuous levels of around 50% of state O), and 'cluster High-O' (consistently high levels of O).

Medication use levels and cluster dynamics

The most dominant state overall is the prescription-free state N. Cluster N, the largest cluster, characterised by the prevalence of state N throughout the observation period, includes patients without significant pharmacologic therapy and accounts for 61.6% of the study population. State N is also the dominant state in clusters M-peak4, M-peak8 and Increase (combined 22.6% of the study population) for significantly more than half of the observation time.

State M is the most frequently observed medication state, particularly present in clusters M, M-peak4, M-peak8 and Increase (collectively 33.7% of the study population). While state M levels vary in clusters M-peak4, M-peak8 and Increase (rates between 11.0% and 87.1%), patients' medication sequences in cluster M are characterised by continuous medication (rates between 69.3% and 80.7%).

Opioid use is primarily concentrated in clusters Medium-O and High-O which together constitute 4.7% of the study population. Cluster High-O exhibits consistently high opioid use (rates between 82.0% and 90.9%), while cluster Medium-O displays monthly medication levels around 50% (rates between 36.74% and 57.5%). The frequency plot of cluster Medium-O reveals that most patients alternate between states with and without prescriptions. Overall, medication levels increase toward the end of the observation period. This increase is most noticeable in cluster Increase, while clusters M, High-O and Medium-O also exhibit modest increases.

Regarding cluster dynamics, clusters N, High-O and M can be classified as stable throughout the observation time, while clusters M-peak4, M-peak-8 and Increase are considered dynamic. Cluster Medium-O occupies a unique position: few patients share the same sequences, but the alternating pattern between state N and state O and the state distribution remain consistent over time.

Patient characteristics by sequence clusters

The patient populations within individual clusters exhibit distinct characteristics (refer to table 2).

Cluster N includes the smallest percentage of women and is marked by relatively low or the lowest comorbidity levels (based on Elixhauser scores, opioid dependence and pain-related diagnoses) and healthcare utilisation concerning physical therapy (40.79%) and THR (41.18%).

The relatively young patients in the Increase cluster predominantly reside in urban areas and exhibit

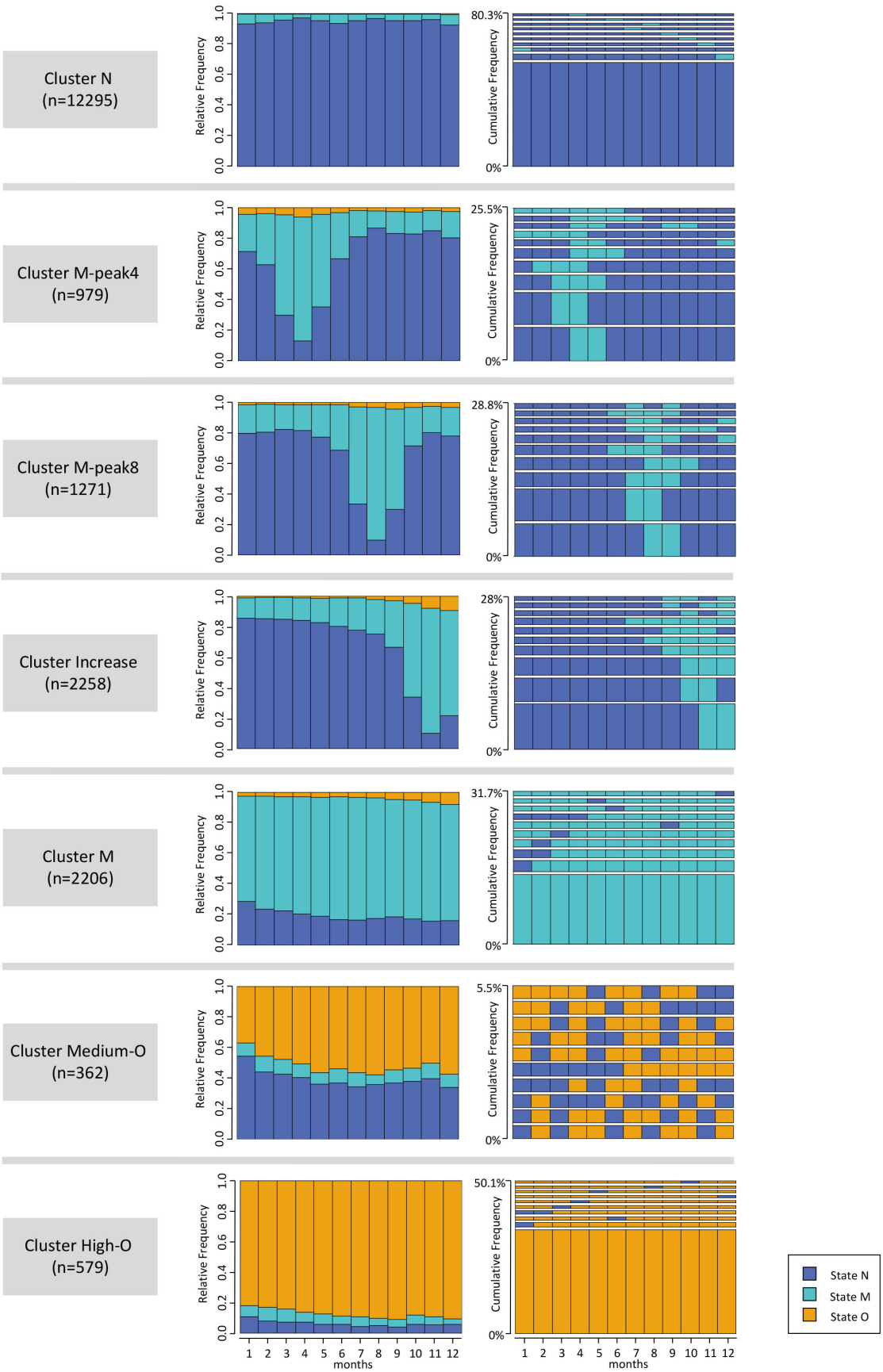

Figure 2 Distribution and frequency plots for each of the seven identified clusters. The distribution plots show the distribution of states in each month of the observation period. The frequency plots show the 10 most frequent sequences in each group. The y-axis shows cumulative frequency; thus, the height of the sequences is relative to their occurrence. State N denotes the state with no prescription, state M with mild analgesic prescription, state O with an opioid prescription.

Table 2 Unadjusted summary statistics by sequence clusters

Cluster	N	M-peak4	M-peak8	Increase	M	Medium-O	High-O	P value
Patients (n, %)	12 295 (61.63)	979 (4.91)	1271 (6.37)	2258 (11.32)	2206 (11.06)	362 (1.81)	579 (2.90)	
Patients (%) aged								
Below 60 years	20.94	21.35	21.40	20.50	21.85	10.50	20.21	
60–69 years	25.70	24.51	27.22	28.12	26.97	15.19	20.55	
70–79 years	37.00	37.69	37.14	36.45	33.86	39.23	33.33	
80 years and older	16.36	16.45	14.24	14.92	17.32	35.08	25.91	0.0001
Mean age	68.71	68.75	68.45	68.60	68.66	74.59	70.71	
(95% CI)	(68.51, 68.91)	(68.04, 69.47)	(67.85, 69.05)	(68.15, 69.04)	(68.20, 69.13)	(73.48, 75.70)	(69.72, 71.70)	0.0001
Women (%)	55.53	61.70	62.08	60.01	61.56	74.59	64.42	<0.0001
Patients living in (%)								
Urban region	27.54	25.03	27.85	30.29	25.02	27.90	23.83	
Region with moderate urbanisation	22.03	23.29	21.24	21.70	22.48	21.82	23.49	
Rural region	50.43	51.69	50.90	48.01	52.49	50.28	52.68	0.02
Mean Elixhauser comorbidity score	0.92	1.27	0.98	1.14	1.17	2.94	2.36	
(95% CI)	(0.86, 0.99)	(1.02, 1.53)	(0.78, 1.18)	(0.97, 1.31)	(0.99, 1.34)	(2.25, 3.63)	(1.87, 2.86)	0.0001
Patients in the following pain category (%)								
Cancer	3.53	4.19	3.15	4.07	3.72	6.63	7.60	<0.0001
Back pain	29.08	38.00	38.47	35.25	38.98	49.45	53.71	<0.0001
Disc prolapse	12.22	17.16	14.71	15.63	13.24	8.84	11.05	<0.0001
Patients with vertigo (%)	14.37	14.40	13.77	14.57	14.87	21.27	12.44	0.012
Patients with opioid dependence (%)	0.04	0.20	0.16	0.09	0.09	0.55	2.25	<0.0001
Patients receiving physical therapy (%)	40.79	56.18	56.57	54.56	53.81	53.31	47.67	<0.0001
Patients undergoing THR (%)	41.18	49.13	62.31	74.62	68.77	42.54	48.88	<0.001

P value comparing patients from THR group and noTHR group using appropriate correlation tests (Pearson's χ^2, Kruskal-Wallis, analysis of variance).
THR, total hip replacement.

significantly higher rates of physical therapy (54.56%) and the highest THR rate (74.62%) compared with the other clusters.

Cluster M patients closely resemble those in the Increase cluster in terms of age, gender, comorbidity and physical therapy rates (53.81%). However, they are more likely to live in less urbanised areas. This cluster has the second-highest THR rate (68.77%).

Patients in clusters M-peak4 and M-peak8 share similar sociodemographic traits with those in cluster M. These two clusters exhibit the highest physical therapy rates, 56.15% and 56.75%, respectively. M-peak4 has a comparatively low THR rate of 49.13%, while M-peak8 has a higher THR rate of 62.31%.

Clusters Medium-O and High-O, with the oldest patients and highest women percentages, show significant differences from other clusters. These clusters exhibit the highest expression for all comorbidity variables and comparatively low THR and physical therapy rates.

Correlation with THR

Using logistic regression, we investigated whether the identified patterns exhibited increased or decreased odds for subsequent THR. The regression analysis (see table 3) revealed that, after adjusting for patient characteristics and morbidity, cluster membership is significantly associated with THR. Cluster Increase demonstrates the strongest association with THR, having fourfold odds compared with cluster N. Cluster M and M-peak8 follow with ORs above 3 and 2, respectively, while High-O and M-peak4 have ORs above 1. Cluster Medium-O displays only a slight, non-significant difference in odds compared with cluster N.

Older and more comorbid patients, as well as those in pain categories above the osteoarthritis pain category, exhibit significantly decreased odds for THR. Patients living in less urban regions also show decreased odds. Patients receiving physical therapy demonstrate increased odds for THR.

Table 3 Results of logistic regression for outcome total hip replacement surgery

Independent variables	OR	95% CI	P value
Age, reference: below 60 years			
60–69 years	0.927	0.850, 1.010	0.084
70–79 years	0.909	0.838, 0.987	0.023
80 years and older	0.486	0.439, 0.538	<0.0001
Gender, reference: male			
Female	1.020	0.960, 1.084	0.521
Residence, reference: urban region			
Region with moderate urbanisation	0.797	0.733, 0.866	<0.0001
Rural region	0.690	0.643, 0.740	<0.0001
Physical therapy, reference: none			
Receiving physical therapy	1.571	1.479, 1.669	<0.0001
Elixhauser comorbidity score	0.982	0.975, 0.990	<0.0001
Pain category, reference: osteoarthritis			
Cancer	0.835	0.712, 0.979	0.026
Back pain	0.855	0.798, 0.916	<0.0001
Disc prolapse	0.816	0.744, 0.894	<0.0001
Opioid dependence, reference: none			
Opioid dependence	1.029	0.471, 2.247	0.943
Cluster membership, reference: cluster N			
Cluster Increase	4.160	3.751, 4.613	<0.0001
Cluster M-peak8	2.278	2.017, 2.572	<0.0001
Cluster M-peak4	1.352	1.183, 1.544	<0.0001
Cluster Medium-O	1.209	0.972, 1.503	0.088
Cluster M	3.204	2.901, 3.539	<0.0001
Cluster High-O	1.540	1.295, 1.831	<0.0001
Constant	0.938	0.854, 1.029	0.175

Area under receiver operating characteristic curve: 67.7%.
CI, confidence interval; OR, odds ratio.

DISCUSSION

In our study, we used SSA on German health insurance data to identify medication patterns for coxarthrosis patients and their correlation with patient characteristics and THR surgery. Our findings revealed seven distinct patterns, with the patient population showing significant differences in demographic, regional and health or healthcare use-related characteristics. Logistic regression showed a strong correlation between cluster membership and THR surgery. Below, we discuss our findings focusing on the recommended use of mild analgesics, a stepped prescription approach, cautious opioid use and the exhaustion of conservative therapy prior surgery.

Four clusters are characterised by the presence of state M: clusters Increase, M, M-peak4 and M-peak8. The medication pattern in all four clusters can be interpreted as a reflection of pain symptomatology.

The significant rise in mild analgesics in cluster Increase can be attributed to rapid disease progression and increasing symptom severity. In contrast, cluster M includes patients with continuous high-level analgesic use, indicating long-lasting and persistent pain. Both clusters do not show any particularly high comorbidity expression, suggesting osteoarthritis drives the medication patterns. This is supported by the high THR rates observed. The increase in opioid use in the final months can be reliably attributed to the goal of bridging the time to surgery, as recommended in guidelines.[1–3] Cluster Increase and cluster M exhibit significant differences in age distribution and residential area. Since urbanity levels influence local healthcare infrastructure,[47] an association between urban patients and high THR rates can be expected, as observed in cluster Increase. Surprisingly, even cluster M, with its more rural population, shows elevated medication use and THR rates.

Logistic regression confirms that these clusters represent two distinct medication use patterns, both leading to THR surgery. Both patterns reflect the exhaustion of conservative medication therapy prior to surgery, as recommended. An intriguing question for future research is whether long-term outcomes after surgery differ between patients with a dynamic movement to surgery, as seen in cluster Increase, and those with prolonged consistent pain management before surgery, as seen in cluster M.

The peaks of state M in M-peak4 and M-peak8 clusters can be attributed to acute pain episodes, typical for the intermittent course of coxarthrosis.[48] The subsequent decrease in medication use may result from symptom improvement, which could occur spontaneously or as a result of changes in lifestyle or physical therapy use. Indeed, the two clusters show the highest rates of physical therapy. Alternatively, the decrease could stem from concerns over long-term analgesic use and associated side effects, leading to reduced medication use despite persisting pain. THR rates and ORs for THR surgery are significantly lower in these two clusters than in the Increase and M clusters, suggesting slower disease progression and less frequent decisions to undergo surgery. However, ORs for THR surgery compared with cluster N are significantly increased in both clusters. Given an appropriate indication for THR surgery, we cannot infer that the low medication rates in the final months of the observation period suggest an equally low level of pain symptomatology in these patients.

The two opioid clusters, Medium-O and High-O, show high long-term opioid use, exceeding recommendations,[2 5] but represent a small fraction of the study population. These patterns may be attributed, at least partially, to other conditions, as indicated by pain and comorbidity variables and an older age demographic. Previous studies link comorbidity and age to opioid use, possibly due to increased NSAID contraindications.[16 19 49] The clusters show low THR rates, potentially because coxarthrosis pain is deprioritised amidst multiple pain conditions and multifactorial immobility. However, given the evidence of higher osteoarthritis burden in patients with higher opioid use,[14] underuse of physical therapy and THR surgery is possible. Future research should investigate whether the reduced utilisation of surgery and physical therapy benefits these older and more comorbid patients or represents treatment underuse.

Overall, in terms of opioid prescription, we found a generally low use of opioids. In clusters Increase, M, M-peak4 and M-peak8 short-term increases in use toward THR surgery or at time of the peaks are visible. Clusters with high opioid use are small and patient's characteristics suggest the presence of other factors causing opioid use. These findings suggest a cautious prescribing of opioids and general adherence to the stepped prescription approach in these clusters, which is consistent with other German studies.[14 19]

It is important to note that the medication use patterns discussed affect less than half of patients, as 61.6% of patients belong to cluster N, which is characterised by the absence of any significant pharmacological therapy. Also in other clusters, clusters M-peak4, M-peak8 and Increase, the prescription-free state N is dominant for large parts of the observation time. While a high prescription rate of analgesics is not desirable per se, this high proportion of patients without significant pain medication raises concerns about whether all patients receive adequate access to and counselling about conservative treatment options. It is unlikely that this proportion of patients without medication reflects an equally high proportion of patients without pain, considering that all patients had a confirmed diagnosis of coxarthrosis prior to the observation period and many patients underwent hip surgery at the end of the observation period (with the lowest rate being as high as 41.18% in cluster N). Thus, we find no evidence of exhaustion of conservative medical treatment options prior THR in a significant proportion of patients. Additionally, the low use of physical therapy, especially in cluster N, suggests the underuse of physical therapy options. Previous national and international studies have raised similar concerns about the use of conservative therapy options.[16 24 50 51]

The logistic regression revealed further that the likelihood for THR surgery decreases with age and comorbidities, consistent with studies showing a clear correlation between these factors and THR surgery rates.[10 16] The increase in complication rates, longer length of stay and higher readmission rates in patients with more comorbidities[52] might discourage physicians from performing surgery in elderly patients, or induce concerns about surgery in elderly patients.[53] In line with previous studies, the logistic regression results show the rural-urban divide[9] and the correlation of THR rates with comorbidities.[16]

Strengths and limitations

The quality criteria for the presented 7-cluster solution indicate a reasonable data structure. Compared with previous studies applying SSA to insurance data, the quality achieved is very good.[26 27 29 30 54] Sensitivity analyses confirm the cluster solution's stability. We used a theory-driven approach to obtain meaningful measures of state dissimilarity and sequence dissimilarity by using a set of state features reflecting the hierarchical nature of prescription states. In doing so, we respond to criticisms levelled at purely data-driven methods.[35]

Our analysis, based on a large dataset from two German health insurance companies, benefits from low selection bias and comprehensiveness. The sizeable population allowed us to establish an expansive study cohort, extend our observation period to a full year and exclusively include patients in the noTHR group who had not undergone surgery for at least 1 year after the observation period.

Health insurance claims also have some limitations, many arising from the fact that they depict only prescribed medications, not actual use. First, WHO Level I analgesics are available in small doses over the counter. Thus, utilisation rates of mild analgesics are likely to be underestimated. However, since health insurers only cover the cost if a prescription is presented, there is an incentive, especially for frequent users, to obtain a prescription. Also, the low physical therapy rates not subject to this limitation confirm the prevailing pattern of low utilisation.

Second, we assumed purchased medications were used immediately after purchase. However, patients may use leftover medications from previous prescriptions, resulting in an underestimation of medication use rates. Conversely, patients can purchase prescribed medications but use less than the entire doses, which could lead to overestimated rates. However, we can reasonably assume that all mentioned scenarios occur on a much smaller scale than the macrolevel picture enabled by our analysis.

Third, we can only see prescriptions redeemed at the pharmacy. Thus, we cannot determine whether underserved patients lack prescriptions or simply have not redeemed them.

Another challenge with claims data is the operationalisation of pain. We addressed this problem by using hierarchical pain categories defined by Freytag *et al* for this purpose.[42]

Finally, health insurance claims data lack clinical and lifestyle information. As a result, imaging findings on joint wear progression, body mass index and physical activity are not available. This also means that non-billable components of arthritis-relevant conservative therapy measures, such as physician-recommended weight reduction or exercise, could not be included in our analysis.

CONCLUSION

In conclusion, using innovative methods like SSA on health insurance claims data enables us to identify, visualise and analyse medication use patterns, providing a comprehensive understanding of care patterns in coxarthrosis patients. Our analysis reveals the heterogeneity of medication use patterns and their strong correlation with sociodemographic and health-related characteristics.

Our findings show cautious opioid prescribing and a gradual prescription strategy in most clusters, in line with guidelines. However, the significant proportion of patients in cluster N, lacking substantial pharmacological therapy, suggests potential underuse of conservative pain management. This is supported by overall low physiotherapy rates. Thus, many patients do not seem to exhaust conservative therapy options before surgery.

Future research should investigate factors determining medication use, reasons for low conservative therapy utilisation and the impact of medication use patterns and surgery timing on long-term outcomes. Our findings underscore the ongoing need for health policy efforts to encourage patients and providers to exhaust conservative therapy options prior surgery.

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Appendix

2.5 Paper I: Supplemental material

Supplemental material: Identifying and investigating ambulatory care sequences before invasive coronary angiography

1. Codes

In the following, the codes for the identification of relevant diagnoses, procedures and medications in insurance claims are detailed:

- Diagnosis of stable CAD in pre-observation period: ICD-codes I20.8, I20.9, I25.0, I25.1, I25.5, I25.8, I25.9
- PCI: OPS-codes 8-837.X, 8-83d.X; EBM-code: 34292
- CABG surgery: OPS-codes 5-361.X or 5-362.X
- Acute coronary event: ICD-codes I20.0, I20.1, I21.X, I22.X, I24.X
- Prognosis-improving medication: ATC-Codes C10AA, C10AB, C10AC, C10AD, C10AX, C10BA, C10BX
- Symptom-oriented medication: ATC-Codes C07, C08, C01DA, C09DB, C09BB, C09BX01, C09BX02, C09BX03, C09DX05, C10BX03, C10BX07, C10BX09, C10BX11, C10BX14, C01EB17, C01EB18

2. Sequence dissimilarity and clustering

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. The assumption made on the cost of an indel or substitution and the balance between indel and substitution cost may affect the outcome of the clustering substantially [1, 2]. 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] as well as for the inability of state transitions to reflect state similarities [2]. We therefore chose a theory-driven approach, characterizing the states by defining attribute variables and using Gower's distance to calculate a substitution matrix [2, 4]. Hereby we aim to approximate the actual state dissimilarity, i.e. the relevance of a change from state A to state B for the patient. This approach is detailed in the following subsection 2.1. Subsequently, the calculation of indel costs and the clustering algorithm are discussed in subsections 2.2 and 2.3.

2.1 Substitution costs

We chose a theory-driven approach to define substitution costs. To this end, the substitution cost matrix is calculated based on the Gower distance [2, 4].

In a first step, a feature matrix of the states was defined which characterizes the states based on the care events. As we defined states based on the binary question of whether the events G, C, P, or S occurred, these events were used as dichotomous attributes for the calculation of the Gower distance between single states. We used the events G, C, S and P as binary variable as features for the states, with value 1 denoting

the occurrence of the corresponding event in this state. Thus, the rows of the feature matrix uniquely identify each state. The entire feature matrix is displayed in table 1:

Table 1. Feature matrix for calculation of the Gower matrix.

state	G	C	S	P
N	0	0	0	0
G	1	0	0	0
C	0	1	0	0
GC	1	1	0	0
GP	1	0	0	1
CP	0	1	0	1
GCP	1	1	0	1
GS	1	0	1	0
CS	0	1	1	0
GCS	1	1	1	0
GPS	1	0	1	1
CPS	0	1	1	1
GCPS	1	1	1	1

Secondly, the Gower matrix, i.e. the substitution cost matrix, was calculated using the seqcost-function from the TraMineR package [5]. The parameters used are the binary feature matrix as displayed in table 1. Further, weights for the features were specified. Features G and C, related to physician consultation were weighted with 0.5 while features P and S were weighted with 1.0. Thereby, we assert that the distance between two states differing in terms of medication should be greater than the distance between two states with the same medication events but different physician events. We thus assume that, from a medical perspective, it is more consequential if a patient receiving symptom-oriented therapy from a general practitioner were instead to receive prognosis-improving therapy from a general practitioner (substitution of state GS with state GP, denoted as GS→GP), than if the patient continues with the same medical therapy but receives the prescription from a physician of a different specialty (GS→CS).
The resulting substitution cost matrix is displayed in table 2.

2.2 Indel costs

To calculate indel costs, we used the localized optimal matching approach (cf. [6, 2]). In this approach, the cost of insertion C_{izj} of state z into a sequence between state i and j (neighbour states) is defined as

$$C_{izj} = x \cdot w_{\max} + y \cdot \frac{w_{zi} + w_{zj}}{2}. \tag{1}$$

Here, $w_{zi/zj}$ denotes the substitution cost (calculated in the previous subsection) between the state to be inserted, z, and state i/j and $w_{\max}$ the maximum of these two costs. x and y are adjustable parameters and can be interpreted as penalization of time warping (''time cost'' x) or differences of the inserted state to the neighbors (''local cost'' y). Following the recommendations of the literature [6, 2], we choose a small spell expansion cost of $x = 0.05$ and $y = 1 - 2x = 0.9$. With this approach, the cost of an indel operation depends on the substitution cost between the inserted/deleted state and its surrounding states. For example, the insertion/ deletion of the state GCSP into an exemplary sequence consisting only of the state N would be assigned greater costs than the insertion of a G or C state in this sequence.

Table 2. Substitution cost matrix calculated with Gower's distance.

	N	G	C	GC	GP	CP	GCP	GS	CS	GCS	GPS	CPS	GCPS
N	0.00	0.17	0.17	0.33	0.50	0.50	0.67	0.50	0.50	0.67	0.83	0.83	1.00
G	0.17	0.00	0.33	0.17	0.33	0.67	0.50	0.33	0.67	0.50	0.67	1.00	0.83
C	0.17	0.33	0.00	0.17	0.67	0.33	0.50	0.67	0.33	0.50	1.00	0.67	0.83
GC	0.33	0.17	0.17	0.00	0.50	0.50	0.33	0.50	0.50	0.33	0.83	0.83	0.67
GP	0.50	0.33	0.67	0.50	0.00	0.33	0.17	0.67	1.00	0.83	0.33	0.67	0.50
CP	0.50	0.67	0.33	0.50	0.33	0.00	0.17	1.00	0.67	0.83	0.67	0.33	0.50
GCP	0.67	0.50	0.50	0.33	0.17	0.17	0.00	0.83	0.83	0.67	0.50	0.50	0.33
GS	0.50	0.33	0.67	0.50	0.67	1.00	0.83	0.00	0.33	0.17	0.33	0.67	0.50
CS	0.50	0.67	0.33	0.50	1.00	0.67	0.83	0.33	0.00	0.17	0.67	0.33	0.50
GCS	0.67	0.50	0.50	0.33	0.83	0.83	0.67	0.17	0.17	0.00	0.50	0.50	0.33
GPS	0.83	0.67	1.00	0.83	0.33	0.67	0.50	0.33	0.67	0.50	0.00	0.33	0.17
CPS	0.83	1.00	0.67	0.83	0.67	0.33	0.50	0.67	0.33	0.50	0.33	0.00	0.17
GCPS	1.00	0.83	0.83	0.67	0.50	0.50	0.33	0.50	0.50	0.33	0.17	0.17	0.00

2.3 Clustering

We used a partitioning around medoids algorithm (PAM) and performed clustering for different values of k, the number of initial medoids (k between 3 and 10) and thus the number of clusters. To determine the optimal number of clusters, we used the quality criterion of the weighted average shilouette width (ASWw).

3. Variable selection for logistic regression

The covariables used in the logistic regression were selected due to their known relevance for the health care of patients with CAD. The operationalization of these variables and the specific reasons for their inclusion are as follows:

- Cluster membership was included to investigate the correlation between identified ambulatory treatment patterns and the presented outcome.
- General patient characteristics (age, gender) were considered due to their known relation to CAD morbidity: it has been shown that CAD incidence, prevalence and mortality, risk factors, prevalence of co-morbidities, perception of CAD symptoms, and CAD-related health care provision differs between men and women [7].
- co-morbidity indices were included in the analysis, since co-morbidity is correlated with higher health care use in general, and might influence patients and/or physicians regarding the decision to perform a re-CA. We calculated the van Walraven-Elixhauser score based on the main hospital diagnoses during the observation time (range: $[-19; 89]$, with higher values indicating a higher or more severe level of co-morbidity) [8, 9]. To account for the co-morbidities of patients without inpatient treatment, we calculated the index based on ambulatory diagnoses over the same time span.
- Regional characteristics were considered, since they have been shown to be correlated with morbidity in general and CAD morbidity and mortality in particular. There are known differences in the health and demographic makeup of the federal states of the former East Germany [10].
- Independent variables depicting health service utilization patterns relevant to CAD morbidity were considered. One variable denotes the patient's enrollment in the structured disease management

program for CAD, which could be related to a higher frequency of visits and a higher probability for CAD specific treatment as well as higher CAD morbidity. Another variable denotes whether the patient received some form of NID in the last sequence quarter, as it is recommended in the treatment guidelines. This variable could possibly relate to medical practice patterns and patient preferences, but also to regional structures, since the necessary equipment might not be equally available across regions.

- A variable was included to denote whether invasive revascularization therapy had been performed in the context of the index CA, operationalized as a PCI or bypass recorded within 30 days of the index CA or in the same billing episode as the index CA. The decision of the patient to undergo revascularization therapy is the main indication for CA in stable CAD patients [11, 12, 13, 14]. Further, evidence suggests that recatheterization may be correlated with whether the index CA was a CA with or without consecutive invasive therapy [15].

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2.6 Paper II: Supplemental material

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:

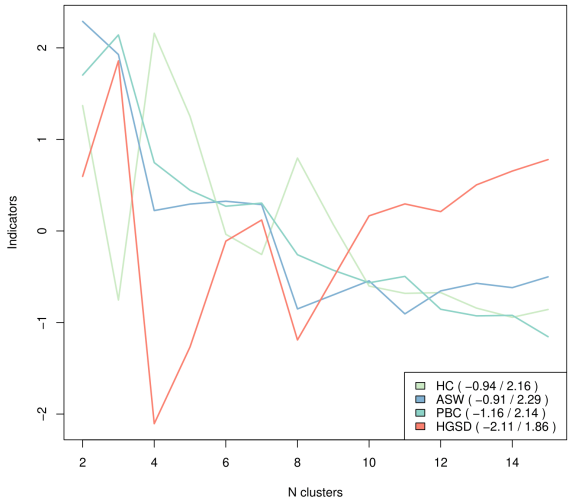

Figure 1. Graphical depiction of normed cluster quality indicators Hubert's C (HC), Hubert's Somers' D (HGSD), Average Silhouette Width (ASW), and Point Biserial Correlation (PBC) for clustering solutions with cluster count (N) ranging from 2 to 15.

- 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

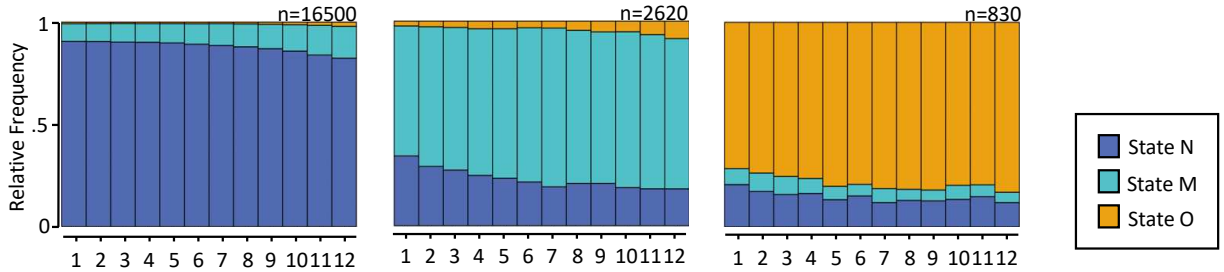

Figure 2. Distribution plots illustrating the 3-cluster solution. The patterns within these three clusters align closely with those observed in clusters N, M, and High-O from the primary analysis.

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"]
```

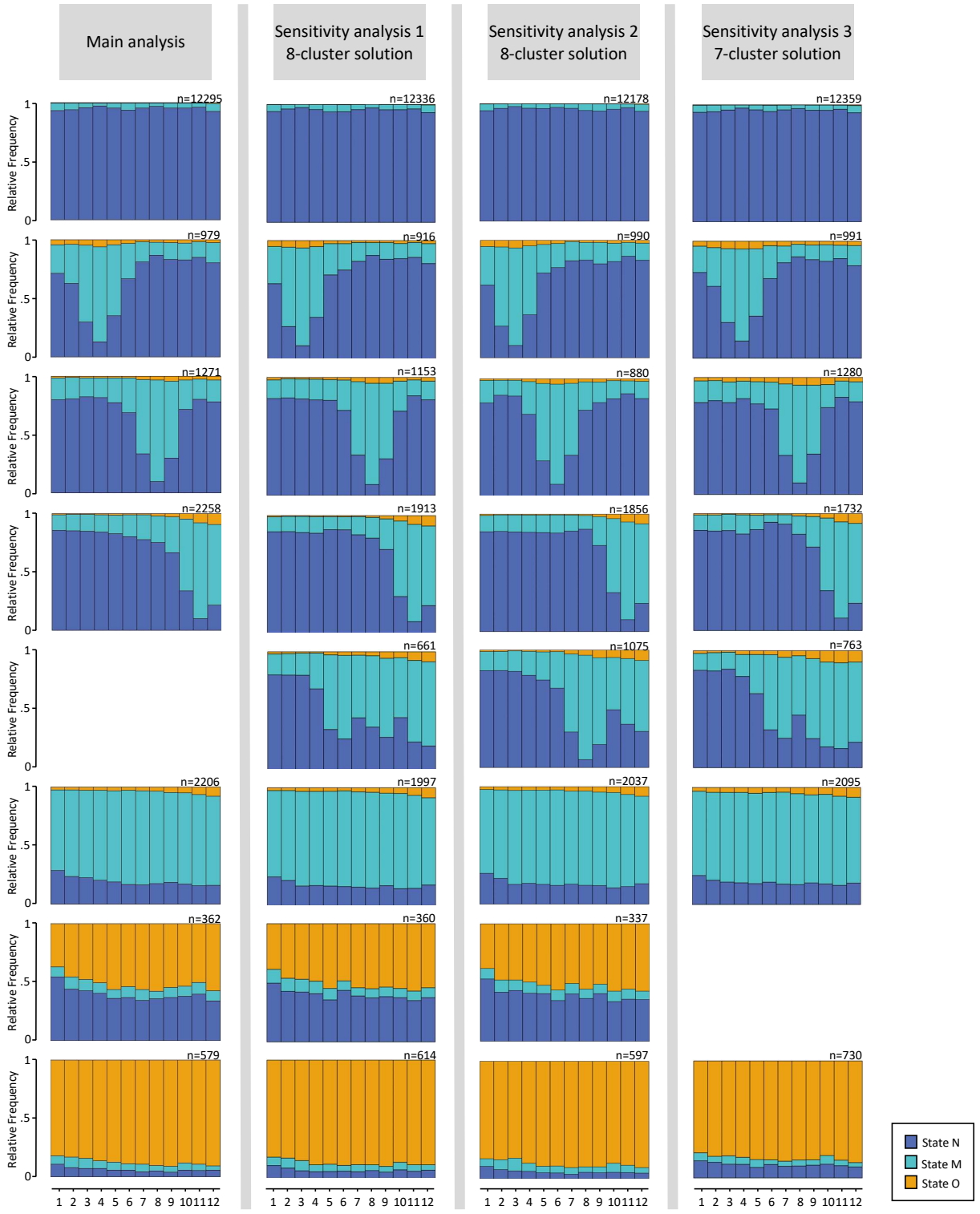

Figure 3. Outcomes of Selected Sensitivity Analyses: Sensitivity analyses 1 and 2 feature newly randomized population for the noTHR group, while Sensitivity analysis 3 incorporates both a re-randomized noTHR group and a bootstrapped THR group. The striking congruity across the cluster solutions underscores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

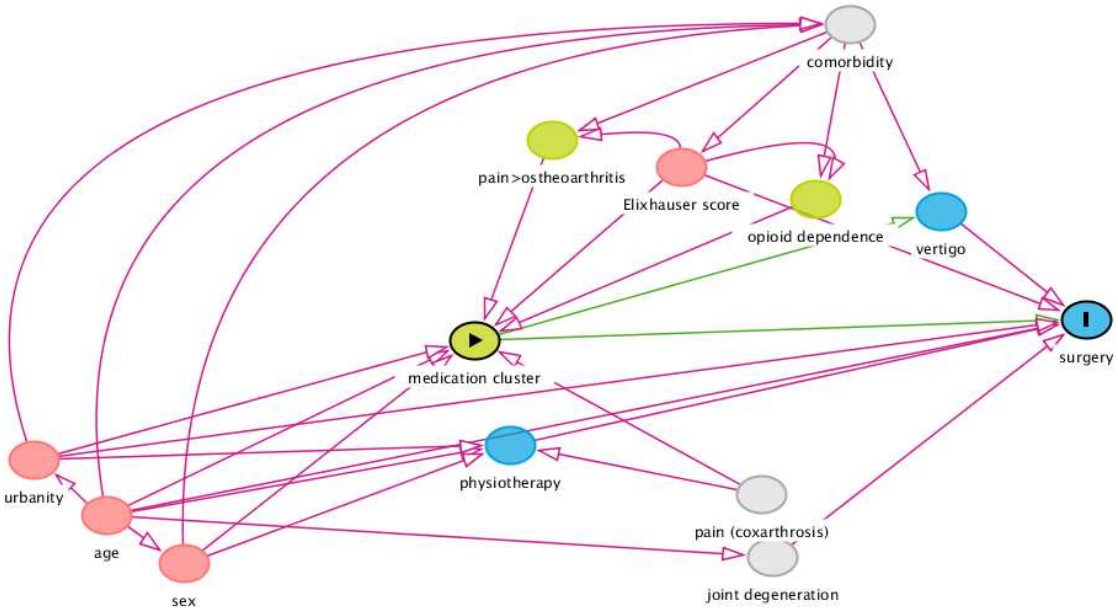

Figure 4. Theoretical model informing logistic regression using directed acyclic graphs (DAG). The figure was generated using dagitty.net [22]. Red nodes denote ancetors of exposures and outcome, yellow nodes ancestors of exposure, blue nodes, ancestor of outcomes, grey nodes unobserved variables. Red 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
}
```

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List of all scientific publications to date

Publications in peer-reviewed journals

1. Bühler C., Novelli A., Flothow A., Sundmacher L. (2025): Exploring Patterns in Pediatric Type 1 Diabetes Care and the Impact of Socioeconomic Status. *BMC Medicine. (Accepted for publication.)*

2. Novelli A., Frank-Tewaag J., Franke S., Weigl M., Sundmacher L. (2024): Exploring heterogeneity in coxarthrosis medication use patterns before total hip replacement: a State Sequence Analysis. *BMJ Open. 14*(9):e080348.

3. Bammert P., Schüttig W., Novelli A., Iashchenko I., Diehl K., Blume M., Spallek J., Sundmacher L. (2024): The role of mesolevel characteristics of the health care system and socioeconomic factors on health care use – results of a scoping review. *International Journal of Equity in Health 23*:37.

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11. Danner M., Geiger F., Wehkamp K., Rueffer J. U., Kuch C., Sundmacher L., Skjelbakken T., Rummer A., Novelli A., Debrouwere M., Scheibler F. (2020): Making shared decision-making (SDM) a reality: protocol of a large-scale long-term SDM implementation programme at a Northern German University Hospital. *BMJ Open 10*(10).

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13. Hoffmann S., Wachtler B., Sander L., Blume M., Hilger-Kolb J., Herke M., Matos Fialho P., Pischke C., Novelli A., Lampert T., Spallek J. (2020). Health inequalities among infants and pre-school children: Protocol for a scoping review examining the moderating and mediating role of contextual and compositional family characteristics. *OpenScience Framework*.

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