

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Exploring heterogeneity in coxarthrosis medication use patterns before total hip replacement: a State Sequence Analysis
AUTHORS	Novelli, Anna; Frank-Tewaag, Julia; Franke, Sebastian; Weigl, Martin; Sundmacher, Leonie

VERSION 1 - REVIEW

REVIEWER NAME	<i>LAMER, Antoine</i>
REVIEWER AFFILIATION	University of Lille, ULR 2694 - METRICS : Évaluation des technologies de santé et des pratiques médicales
REVIEWER CONFLICT OF INTEREST	No competing interests
DATE REVIEW RETURNED	18-Jan-2024

GENERAL COMMENTS	<p>The authors aim to provide a comprehensive understanding of the healthcare trajectories of patients with coxarthrosis before undergoing total hip replacement (THR) surgery. They seek to identify and visualize patterns in medication usage among these patients, exploring the associations with patient characteristics and THR. Additionally, the study compares these patterns with recommendations regarding mild analgesics, opioid prescriptions, and the exhaustion of conservative therapy. The overarching goal is to shed light on the care of coxarthrosis patients pre-THR and investigate whether particular medication patterns are linked to the eventual need for THR.</p> <p>The study reveals diverse medication usage patterns strongly correlated with sociodemographic and health-related factors. While cautious opioid prescribing aligns with guidelines, a notable cluster (Cluster N) indicates potential underuse of conservative pain management, supported by low physiotherapy rates. This suggests that many patients may not fully explore conservative therapy before opting for surgery. Future research should explore factors influencing medication use, reasons for limited conservative therapy utilization, and the impact of medication patterns and surgery timing on long-term outcomes. The findings emphasize the ongoing necessity for health policy efforts to promote the thorough exploration of conservative therapy options before resorting to surgery by patients and healthcare providers.</p> <p>The manuscript is of very high quality. The introduction provides all the necessary elements to understand the context. The method is comprehensive and well-written, in coherence with the presentation of results. Finally, the discussion provides insights to comprehend the results. The study's limitations, specifically biases associated with the use of medical-administrative databases, are clearly explained.</p>
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	<p>I have only a few minor comments that could enhance readability and provide additional information for the reader.</p> <p>1) In the introduction, you state : "Furthermore, the observed geographical variation in THR rates raises questions about the appropriateness and timeliness of the decision for THR surgery". Could this geographical variation be related to differences in hospital practices? Perhaps influenced by local recommendations or established practice habits?</p> <p>2) "Our analysis used comprehensive data from two German statutory health insurers, AOK Bayern and SBK. The 10 data, spanning 2012-2015, includes reimbursable claims, diagnoses, and demographics for individuals aged 11 18+ diagnosed with coxarthrosis in 2012." Could you please explain the inclusion criteria in both the AOK Bayern and SBK databases? Is it based on geography, the insured individual's profession, or the insured individual's choice? Are there differences in reimbursement for services, particularly in the dispensing of medications, between these two databases?</p> <p>3) "Both groups are included when a coxarthrosis diagnosis was documented in 2012." Would it have been relevant to include them in the initial diagnosis, with a washout period for the preceding years (i.e., without the presence of the diagnosis in 2010 and 2011, for example)?</p> <p>4) "based on the daily defined dose". Is this daily defined dose documented in the database for each drug delivery, with the quantity of the drug packaging, or was it defined by experts for each molecule ?</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer's comments:

The authors aim to provide a comprehensive understanding of the healthcare trajectories of patients with coxarthrosis before undergoing total hip replacement (THR) surgery. They seek to identify and visualize patterns in medication usage among these patients, exploring the associations with patient characteristics and THR. Additionally, the study compares these patterns with recommendations regarding mild analgesics, opioid prescriptions, and the exhaustion of conservative therapy. The overarching goal is to shed light on the care of coxarthrosis patients pre-THR and investigate whether particular medication patterns are linked to the eventual need for THR.

The study reveals diverse medication usage patterns strongly correlated with sociodemographic and health-related factors. While cautious opioid prescribing aligns with guidelines, a notable cluster (Cluster N) indicates potential underuse of conservative pain management, supported by low physiotherapy rates. This suggests that many patients may not fully explore conservative therapy before opting for surgery. Future research should explore factors influencing medication use, reasons for limited conservative therapy utilization, and the impact of medication patterns and surgery timing on long-term outcomes. The findings emphasize the ongoing necessity for health policy efforts to promote the thorough exploration of conservative therapy options before resorting to surgery by patients and healthcare providers.

The manuscript is of very high quality. The introduction provides all the necessary elements to understand the context. The method is comprehensive and well-written, in coherence with the presentation of results. Finally, the discussion provides insights to comprehend the results. The

study's limitations, specifically biases associated with the use of medical-administrative databases, are clearly explained.

Response: We thank you for the thorough review and the positive evaluation.

I have only a few minor comments that could enhance readability and provide additional information for the reader.

1. In the introduction, you state: "Furthermore, the observed geographical variation in THR rates raises questions about the appropriateness and timeliness of the decision for THR surgery". Could this geographical variation be related to differences in hospital practices? Perhaps influenced by local recommendations or established practice habits?

Response: Thank you for your comment. Indeed, supply-side factors such as provider density, proximity to hospitals, and regionally prevailing medical practices and treatment paradigms may contribute to the observed geographical variation in THR rates. In the beginning of the introduction, we mention that '[d]espite their availability, significant regional variations in total hip replacement (THR) rates have been observed in Germany⁹ and internationally¹⁰⁻¹², which cannot be fully accounted for by morbidity differences in the population. This indicates the existence of non-morbidity-related factors influencing treatment decisions for coxarthrosis patients, potentially leading to deviations from guidelines.' Taking your comment into account, we have now replaced the second sentence with a more detailed description of the possible factors:

(...) 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. (main document, p.4 l.6-10)

2. "Our analysis used comprehensive data from two German statutory health insurers, AOK Bayern and SBK. The data, spanning 2012-2015, includes reimbursable claims, diagnoses, and demographics for individuals aged 18+ diagnosed with coxarthrosis in 2012." Could you please explain the inclusion criteria in both the AOK Bayern and SBK databases? Is it based on geography, the insured individual's profession, or the insured individual's choice? Are there differences in reimbursement for services, particularly in the dispensing of medications, between these two databases?

Response: Thank you for your question. In principle, every individual in Germany is free in the choice of their health insurance. There is a geographical limitation, as not all insurance companies operate nationwide; some are limited to specific regions. The AOK, for instance, operates across the country but has a regional substructure. Thus, in the AOK Bayern, whose data we use in this project, only residents of the Bavaria region are insured. The Siemens Betriebskrankenkasse (SBK) is a national health insurance associated with the Siemens company but is available to all individuals in Germany. All statutory health insurances have a comprehensive mandatory reimbursement catalog. Their services differ only in limited, additional voluntary services, such as the reimbursement of travel vaccines or bonus programs. The services related to the care events included in our paper's analysis and their reimbursement are consistent across all statutory health insurances.

We included more details on the insurances and their services and reimbursement in paragraph 2.1.

The first sentences of this paragraph read now as follows:

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 analyzed in this study.

(p.6, l.10-14)

3. "Both groups are included when a coxarthrosis diagnosis was documented in 2012." Would it have been relevant to include them in the initial diagnosis, with a washout period for the preceding years (i.e., without the presence of the diagnosis in 2010 and 2011, for example)?

Response: Thank you for your comment. We can follow your reasoning very well. Generally, it is an appealing concept to represent the care pathways of a patient population from the onset of illness to the occurrence of the outcome or care event.

Our study design was influenced by our research focus and the limitations that arise from data protection and data availability. We believe that including a wash-out period of 1 or 2 years is not entirely suitable or feasible for our study:

- Since the progression of coxarthrosis can span several years and the diagnosis of coxarthrosis is complex, often being established late (Bijlsma 2011), to determine the onset of the condition is generally challenging. This is especially true in health insurance claims data, where medical information on the stage of disease progression is lacking. Additionally, because disease progression is marked by acute and quiet phases that can last for extended periods (Bijlsma 2011), a relatively long wash-out period would be necessary, which pushes the limits of data availability.
- Our study design includes a group of patients who undergo hip surgery within the observation period. If we were to limit our focus to patients who receive their first diagnosis after a 1–2-year wash-out period, we would firstly have significantly fewer patients in the surgery group and, secondly, might introduce a selection bias, as the surgery group would predominantly include patients who exhibit a very rapid disease progression.
- Instead of focusing on identifying the onset of the disease, our study design aims to ensure that the patient has been in contact with the healthcare system and is known to doctors as a coxarthrosis patient. For this purpose, the year 2012 is used, in which patients must have received a confirmed diagnosis of coxarthrosis to be included in the study population. This population, whose condition is known, is suitable, in our opinion, to investigate the aspects of the guidelines we focus on in our analysis (i.e., 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). This can be analyzed and visualized regardless of how long the patient has been sick. Our results indicate that symptom severity plays a major role in treatment decisions.

(Reference used: Bijlsma J, Berenbaum F, Lafeber F. Osteoarthritis: an update with relevance for clinical practice. *The Lancet* 2011. 377 (9783) 2115-2126. doi.org/10.1016/S0140-6736(11)60243-2.)

4. "based on the daily defined dose". Is this daily defined dose documented in the database for each drug delivery, with the quantity of the drug packaging, or was it defined by experts for each molecule?

Response: Thank you for your comment. Yes, the daily defined dose is documented in the prescription dataset we used. We elaborated the description of the data used in section 2.1. Data, sample and observation period to include more details on the prescription dataset. The respective paragraph reads now as follows:

(...). The data, spanning 2012-2015, includes reimbursable claims entailing prescriptions, 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. (p.6 l.14-17)