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Evaluation of medical services and health care programs using insurance claims data

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Dedicated to my son Philip

Affidavit

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I hereby declare, that the submitted thesis entitled:

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List of abbreviations

AOK	Allgemeine Ortskrankenkassen
ATC	Anatomical Therapeutic Chemical codes
BKK	Betriebskrankenkasse
DRG	Diagnosis related groups
ICD-10	International Classification of Diseases, 10th Revision
IPF	Idiopathic pulmonary fibrosis
ILD	Interstitial lung disease
IPTW	Inverse probability of treatment weighting
PZN	Pharmazentralnummer/National product codes
RCT	Randomized controlled trial
RWE	Real-world evidence
SHI	Statutory Health Insurance

List of publications

No.	Title	Author	Journal	Impact factor	Rank
1	Cost effects of a health coaching in children and adolescents with mental health and developmental disorders	Pavo Marijic Monika Murawski Werner Maier Karina Hamacher Otto Laub Martin Lang Eva Grill Lars Schwettmann	Academic Pediatrics	3.107	32/129
2	Effects of Influenza Vaccination in Patients with Interstitial Lung Diseases: An Epidemiological Claims Data Analysis	Pavo Marijic Larissa Schwarzkopf Werner Maier Franziska Trudzinski Lars Schwettmann Michael Kreuter	Annals of the American Thoracic Society	6.831	10/64
3	Pirfenidone vs. nintedanib in patients with idiopathic pulmonary fibrosis: a retrospective cohort study	Pavo Marijic Larissa Schwarzkopf Lars Schwettmann Thomas Ruhnke Franziska Trudzinski Michael Kreuter	Respiratory Research	5.631	14/64

1. Your contribution to the publications

1.1 Contribution to paper I

The paper was written within the German Innovationsfonds project “PrimA-QuO – Optimierte primärärztliche Versorgung von Kindern und Jugendlichen mit psychischen Auffälligkeiten und Störungen". The research question was developed by Pavo Marijic in coordination with Lars Schwettmann and Monika Murawski. Pavo Marijic was responsible for the entire data management, developed the analysis strategy, and carried out the analyses in coordination with Lars Schwettmann and Monika Murawski. Pavo Marijic wrote, edited, and reviewed the manuscript and acted as the corresponding author. All co-authors contributed by editing the manuscript.

1.2 Contribution to paper II

The paper was written within the project “ECOMILD II – Economic measurements in ILD” funded by the charitable foundation Stiftung Oskar-Helene-Heim (OHH). The project was initiated by Michael Kreuter and Larissa Schwarzkopf. Pavo Marijic was responsible for the entire data management, developed the analysis strategy, and carried out the analyses in coordination with Michael Kreuter, Larissa Schwarzkopf, Lars Schwettmann, Werner Maier, and Franziska Trudzinski. Pavo Marijic wrote, edited, and reviewed the manuscript and acted as the corresponding author. All co-authors contributed by editing the manuscript.

1.3 Contribution to paper III

The paper was written within the project “ECOMILD II – Economic measurements in ILD” funded by the charitable foundation Stiftung Oskar-Helene-Heim (OHH). The project was initiated by Michael Kreuter and Larissa Schwarzkopf. Thomas Ruhnke prepared the health insurance claims data of the AOK Research Institute on anonymized data sets and executed the secure file exchange to the Helmholtz Zentrum München. Pavo Marijic was responsible for the entire data management after the data transfer from the AOK Research Institute, developed the analysis strategy, and carried out the analyses in coordination with Michael Kreuter, Larissa Schwarzkopf, Lars Schwettmann, and Franziska Trudzinski. Pavo Marijic wrote, edited, and reviewed the manuscript and acted as the corresponding author. All co-authors contributed by editing the manuscript.

2. Introductory summary

2.1 Background

2.1.1 Real-world evidence and claims data

Randomized controlled trials (RCTs) are still the gold standard for evaluating the effectiveness of treatments. However, analysis of longitudinal health care data has recently been receiving increasing attention in medical research (1-3). The use of health care data for generating evidence outside of RCTs is termed real-world evidence (RWE) (4). Considering their broad perspective on health care under real-life conditions, health insurance claims data (hereafter "claims data") represent an important source of RWE. Besides claims data, real-world data include electronic health records, registry data, but also data from cohort studies (4).

The increasing importance of claims data for research in Germany is reflected in a growing number of claims data studies (5, 6). Statutory health insurance (SHI) funds' rising awareness of the potential of claims data for decision-making and increased political funding and support from the German government have influenced this increasing use (5). In this context, three factors pushing the use of claims data for evidence generation in Germany have to be pointed out: First, the German government and the Federal Joint Committee (Gemeinamer Bundesausschuss, G-BA) initiated the "Innovationsfonds" and endowed it with 200 million Euro per year (7). Second, a Health Data Lab (German: Forschungsdatenzentrum Gesundheit), which combines the data from all German SHI funds, was established with the aim of providing real-world data for scientific purposes (8). Currently, most studies are based on data from only one or a few SHI funds, as the data are stored within the data warehouse of each SHI fund. Third, the German National Cohort (NAKO Gesundheitsstudie), a German cohort study including 200,000 participants, links claims data to primary survey data, which will increase the future use of claims data in epidemiological studies (9). There is a broad and ongoing discussion of how RWE, and thereby claims data, can be used in the decision-making of stakeholders (1, 10-12).

2.1.2 Aims of the thesis and included manuscripts

The aim of this thesis was to evaluate medical services and health care programs based on German claims data. Within three exemplary papers, the focus was placed on data-inherent and research question-specific methodological challenges.

In Paper 1, we evaluated the impact of a health coaching program provided by pediatricians for children and adolescents with mental health and developmental disorders (13). The intervention was initiated by a German SHI fund (BKK-Betriebskrankenkassen), which insured about 2.5 mil-

lion individuals in Bavaria in 2020 (19% of Bavaria's population) (14) with the aim of strengthening the role of pediatricians and standardizing treatment (15, 16). Our analyses investigated the impact of the health coaching on subsequent costs of care and demonstrated that the add-on provision of this intervention did not increase overall costs but was associated with a cost shift between the cost of specialized care and the cost of pediatric care.

Papers 2 and 3 examined distinct management strategies in patients with interstitial lung diseases (ILD) based on data provided by the Allgemeine Ortskrankenkassen (AOK), which insured approximately one third of the German resident population (about 27 million in 2020) (17). Paper 2 compared ILD patients with and without influenza vaccination in terms of mortality and hospitalization during four influenza seasons (18). Although ILD patients comprise a vulnerable group, which ought to be vaccinated every year, quantitative information on the benefits of vaccination is lacking (19). Our study unveiled a higher survival probability of vaccinated patients, while no differences were observed in hospitalizations.

In Paper 3, we contrasted mortality, hospitalizations, and costs of care among patients with idiopathic pulmonary fibrosis (IPF) treated with two distinct guideline-recommended antifibrotic drugs (pirfenidone and nintedanib) to explore a potential preference for one or both drugs (20). So far, there is no conclusive evidence in this regard as RCTs comparing both drugs are lacking and evidence provided by observational studies is also sparse (21). The study revealed no relevant differences considering mortality, hospitalizations, and health care costs.

In the following sections, I discuss the use of claims data for treatment evaluation according to the following structure. Section 2.2 presents information on claims data-based treatment evaluation, including a brief description of the German SHI system (2.2.1), advantages and challenges of claims data (2.2.2), and information on non-randomized settings. In section 2.3, selected methodological approaches for claims data-based treatment evaluation are described. Thereby, I discuss the definition of the study population (2.3.1), group assignment and follow-up (2.3.2), confounder adjustment (2.3.3), and the definition of outcome variables in claims data (2.3.4). In section 2.4, a brief summary and a final outlook are provided.

2.2 Claims data-based treatment evaluation

2.2.1 Brief description of the German SHI system

In Germany, health insurance is mandatory and membership of SHI funds is open to everyone, regardless of factors such as occupation, income, age, or medical conditions (22). SHI is provided by 97 competing and self-governing SHI funds, which insured about 88% of the German resident

population in 2020 (about 73 million individuals) (17, 23). The majority of the remaining population is insured with private health insurance funds, while a small share of individuals is insured through specific governmental schemes (e.g., soldiers, refugees) (22). SHI is financed via income-dependent, risk-independent contributions (22) and offers access to a wide range of services with no or only small copayment. Data on all services provided are routinely stored at the SHI funds, which provides a rather comprehensive picture of the utilization of health care services in the cross-sectional but also in the longitudinal view. SHI data include data on socio-demographics, inpatient services, outpatient services, pharmaceuticals, rehabilitation, medical aids (e.g., crutches, wheelchairs), remedies (e.g., physiotherapy, occupational therapy), and information on sick leave.

2.2.2 Analyzing claims data: Advantages and challenges

Claims data studies enable the inclusion of patients who are often excluded from RCTs (e.g., chronically ill individuals, children, elderly patients) or allow subgroup analyses, which are also rarely possible in RCTs on account of small sample sizes. In addition, in some instances, a RCT is hardly feasible, especially when considering rare diseases, rare outcomes, or ethical concerns. The papers included in this thesis addressed rare outcomes such as specialized care utilization of children and adolescents with mental health disorders (Paper 1) or rare diseases such as ILDs or IPF (Papers 2 and 3). Additionally, RCTs provide only limited evidence on long-term outcomes, whereas claims data studies have long observation periods and allow longitudinal analyses.

Detailed and easily accessible utilization and cost information offers an additional advantage for health economic studies. Hence, the use of claims data avoids the influence of recall bias and non-response bias that could occur when information on costs and utilization of services is collected through patient questionnaires (24, 25). The data structure of claims data is beneficial for treatment evaluation as information is often available on a date basis. This has important advantages as the dates of the treatments can be assessed precisely and the temporal component of interventions and outcomes can be determined. Furthermore, claims data do not have to be collected, as they are available as a result of billing processes, which leads to lower costs compared with primary data collection (26). However, this also represents a disadvantage of claims data. As they are not collected for scientific purposes, quality assurance procedures do not necessarily take place in the process of data collection, which is however state of the art for primary data-based studies (27). This makes quality processes in studies using claims data even more important. Consequently, guidelines for ex post quality assurance have been developed (28).

The definition of the study population marks another challenging aspect of claims data. Although survey studies or RCTs select their study population based on clear inclusion criteria, which can be validated by patient or physician records, defining the study population based on claims data is difficult, as there is no means of external validation. This is a specific methodological challenge in claims data and will be discussed further in section 2.3.1. Furthermore, lifetime incidence cannot be assessed and, if patients have longer diagnosis-free intervals, the incidence might be overestimated (29). In addition, there might be an underreporting of diagnosis and procedures, which are not relevant for compensation as they are not coded by the service provider (30). Even though utilization and cost information are detailed in claims data, survey studies offer the opportunity to include study-tailored utilization and costs information such as costs covered by the patient, whereas claims data offer standardized reimbursement-driven documentation and therefore rely on the payers' perspective. Furthermore, there is a lack of important variables in claims data. Here, the missing information on clinical data (e.g., laboratory tests, severity of disease, symptom scores) or patient-reported outcomes (e.g., quality of life) has to be mentioned. This results in a limited ability to control for confounding, which is another crucial methodological aspect of claims data studies and will be discussed further in section 2.3.3.

2.2.3 Non-randomized setting

In contrast to RCTs, most claims data studies have no random treatment allocation and are therefore non-randomized studies. Even though claims data could be linked with data from RCTs, the use of claims data is important precisely when RCTs are not feasible, which was also the case in all the papers included in this thesis.

Random treatment allocation in RCTs ensures that the treatment status is unconfounded with measured or unmeasured baseline characteristics (31). Hence, a direct estimation of the effects of treatment on outcomes between treated and untreated participants is possible (32). In non-randomized studies, treatment assignment is often influenced by the characteristics of the participants, which leads to systematically different baseline characteristics between the groups. Thus, non-randomized studies require complex study designs and methods to account for the possible group differences. Considering that design-related bias can be induced and that there are no analytical methods to fix any flaws in study design, the implementation of an appropriate study design is essential. In recent years, the "target trial framework" has gained importance in non-randomized studies, which postulates the aim of emulating the design of a hypothetical RCT and enabling the estimation of causal effects if the study design is conducted correctly (33-36).

2.3 Selected methodological considerations for claims data-based treatment evaluation

This section discusses selected methodological considerations evaluating treatments when using claims data. Emphasis is placed on crucial aspects that are particularly challenging in claims data studies, such as defining the study population, determining the start of follow-up and treatment assignment, dealing with confounding, and creating outcome variables.

2.3.1 Definition of the study population

The definition of study populations in German SHI data is mostly based on diagnoses from the International Classification of Diseases, 10th Revision (ICD-10). However, keeping the accuracy of coding, possible miscoding, or the length of the observation period of the study (29, 30, 37) in mind, there are ongoing discussions as to how to mitigate the risk of falsely classifying patients as diseased (29, 38, 39).

For Paper 1, the diagnoses for mental and developmental disorders were determined by the creators of the health coaching program. However, to further minimize the risk of identifying false-positive patients, we restricted the population to patients receiving a confirmed diagnosis from a treating pediatrician in the outpatient setting. For Paper 3, we selected the study population based on treatment with one of the two drugs investigated. To identify IPF patients with antifibrotic treatment, we used Anatomical Therapeutic Chemical (ATC) codes in the first place and tradenames (national product codes/Pharmazentralnummer—PZN) in the second place as one or both drugs were also licensed for the treatment of patients with non-small-cell lung cancer. Furthermore, the patients had to have at least one confirmed IPF diagnosis, which was identified via ICD-10 codes. In Paper 2, we used a previously applied algorithm to minimize the risk of false-positive classification as ILD patients (40, 41). The algorithm relied on multiple requirements such as the specialty of the physician who assigns the diagnosis, diagnostic procedures during treatment, and plausibility of the diagnostic patterns.

Although we defined the population carefully and rigorously, we have no information on the specificity and sensitivity of the algorithms applied at all. Therefore, misclassification might be present, which might influence the validity and generalizability of the results. Missing information on sensitivity and specificity in population selection is an important issue in claims data studies that needs to be given greater attention. One possibility in this context would be to link claims data with other data sources such as electronic health records or cohort studies to validate selection processes. The resulting selection algorithms could then be used for studies that only use claims data. Even though we were not able to apply this in our papers, these and other opportunities need to be exploited more intensively.

2.3.2 Follow-up and group assignment

The clear definition of treatment onset and thus the beginning of follow-up is essential for the study design in non-randomized studies and helps to avoid biases if it is conducted correctly (42). As information in claims data is often available on a date basis, the date of intervention, and therefore the start of follow-up, can be determined precisely. The assignment to the intervention group is also mostly clear and based on the investigated intervention, while the control group could be an active comparator or no treatment. An active comparator was shown to reduce the risk of unmeasured confounding in pharmaceutical studies and should always be preferred if available (10, 43). This was the case in Paper 3, where we compared two drugs for the same indication. To determine the group assignment and the start of follow-up, the first prescription of either drug was used. In Papers 1 and 2, no active comparator was present. Thus, it was challenging to determine the start of follow-up for the control group as no clear date was available. Therefore, we used a rolling cohort design in combination with two different matching approaches in both studies to determine a start of follow-up for the control groups. For the rolling cohort design, we started at a certain time point, which marked the beginning of the observation time. Then, we matched patients receiving the intervention with control patients without treatment. This was done for all subsequent time points until the end of the observation time. Afterwards, the matched populations at all time points were combined into one complete data set. Although we decided to use a rolling cohort design in combination with matching to handle the undefined assignment date in the control group, there are also other methods that could be used such as marginal structural models (44) or other longitudinal matching methods (45). In Paper 1, we matched patients using the rolling cohort design based on quarters, as we performed a cost analysis, and the outpatient costs were available on a quarterly basis only. We matched patients treated with untreated patients one quarter after the other and combined all separately matched quarters for the complete study population. Patients were included in the treatment group if they received the health coaching. In Paper 2, the day of the influenza vaccination marked the beginning of follow-up and treatment assignment. Here, the matching for the rolling cohort design was day-based for each season separately, as the seasons were analyzed separately.

2.3.3 Confounder adjustment

As described above, non-randomized studies have no random treatment allocation, and additional methods are necessary to adjust for differences in baseline characteristics. There are mul-

tiple ways to control for confounding in non-randomized studies such as regression models, instrumental variables (46, 47), difference-in-differences approaches (48, 49), weighting methods (50, 51), or matching methods (52, 53), to name just a few. The methods are not always opposing and can often be used complementarily. In the included papers, different matching approaches and a weighting approach were applied.

In Paper 1, a 1:1 propensity score matching was performed to adjust for confounding. The propensity score is used to balance the treatment and control groups by reflecting the probability of assignment to the treatment group conditional on the baseline covariates—irrespective of de facto receipt of treatment (31). As the true propensity score is not known in non-randomized studies, it has to be estimated with observed baseline characteristics. Similar propensity scores are expected to represent similar values in baseline variables and therefore can be considered comparable (54). Thus, differences in outcomes can be attributed to the treatment, but only if all confounders are measured. With the matching in Paper 1, we formed matched sets of treated and control patients with similar propensity scores.

The propensity score can be used in multiple ways including matching, but also for weighting in stratification or as a covariate in a regression model (31). In Paper 3, we used the propensity score for stabilized inverse probability of treatment weighting (IPTW). IPTW weights by the inverse probability of receiving treatment, whereas the propensity scores are used directly to create the weights (55). Stabilized weights, which were used, represent a solution to avoid the impact of extreme weights. The advantage of IPTW in comparison with matching is that all eligible subjects remain in the analysis and are not disregarded, as is often the case in matching approaches (56). As our study population included a rare disease, it was important to avoid the exclusion of patients.

In Paper 2, we also performed matching in combination with the rolling cohort design. However, in this case, we performed an exact matching, which is another very powerful matching approach with the major benefit that the patients matched have exactly the same information on the variables included (52, 57). However, a disadvantage of exact matching is that patients are disregarded if they cannot be matched and, as the information has to be the same, the probability of exclusion gets higher with the inclusion of additional variables. In Paper 2, approximately 25% of the eligible vaccinated patients were excluded because of this matching approach for the benefit of a homogeneous population for the estimation of the treatment effect. Further details of the methods included are described in the papers.

However, all these approaches can only control for observed heterogeneity, whereas randomization is considered to prevent heterogeneities in both observed and unobserved variables. It is

not possible to estimate a causal effect if unobserved heterogeneity persists, which we cannot exclude in the included papers.

One other basic decision for confounding adjustment is the inclusion of the variables that should be considered, which represents a major challenge in claims data studies. Variables should be included if they are related to the outcome and/or the treatment assignment (58-60). As mentioned above, clinical data or data on socio-economic status are often missing in claims data studies. Hence, we often rely on proxy variables to adjust for confounding. One example of this are indices of multiple deprivation, which were used in two papers as a proxy for individual socio-economic background based on the residential area of the patient (61, 62). Furthermore, it is necessary to consider the lack of certain information such as the stage of the disease in the selection of the population to avoid bias. In Paper 1, for instance, we only included children with a first diagnosis of mental health or developmental disorders. Even though we were not able to determine the stage of the disease, we thus tried to include only patients with an incident diagnosis to decrease confounding. This, of course, does not resolve the issue of confounding by indication (i.e., severity of the disease), which marks a common and important limitation in claims data studies. In addition, the challenges in the estimation of incident diseases, which were mentioned in section 2.2.2, have to be considered. In Paper 3, a similar approach was taken by including only patients with initiation of new treatment, because information on treatment initiation would be missing if we included patients already taking drugs at baseline. This distinction is called prevalent vs. incident users and marks an important step to avoid bias. Bias can be induced as prevalent users might be survivors of early treatment, which can induce bias if the risk varies with time, and also treatment might influence the baseline variables, which might introduce confounding (63).

2.3.4 Outcome variables

We evaluated the treatments in the papers by considering multiple outcomes such as mortality, hospitalizations, and costs. Mortality and hospitalizations were analyzed in Papers 2 and 3. Information on both outcomes is available on a date basis and allowed us to perform time-to-event analyses. In addition to all-cause hospitalization, claims data enabled us to investigate specific disease-related hospitalizations. Hence, we analyzed differences in respiratory-related hospitalizations, which we defined based on specific ICD-10 diagnoses.

A cost analysis was performed in Papers 1 and 3. Claims data allow us to perform detailed cost analyses. However, information on expenses varies considerably based on the setting and is of-

ten only available on an aggregated level. For instance, although the cost information for pharmaceuticals in the outpatient setting is very detailed and available for each package retrieved, we have no information on pharmaceutical costs during a hospital stay. Here, the billing is done via diagnosis related groups (DRGs), which is a sum reflecting the overall expenses of a hospital stay, including pharmaceutical treatment. This concerns all cost information during a hospital stay. Another example concerns the outpatient setting. Here, outpatient physician services are billed on a quarterly basis and expenses are aggregated accordingly, whereas cost information for inpatient services is available per hospital stay and therefore date-based. The aggregation makes it challenging to calculate the expenses for a specific time frame or to link it to specific interventions. Therefore, mostly aggregated cost categories are used for the analysis in claims data studies. In Paper 1, we calculated costs based on facilities, departments, where the services were provided, and the physicians' specialty because we wanted to identify specialized care costs. In addition, we calculated remedies, including the cost of speech therapists and occupational therapists, as these were considered to be affected by the intervention. In Paper 3, we examined total costs with subcategories of inpatient costs, outpatient costs, and pharmaceuticals, as well as disease-related costs, which were identified via ICD-10 codes.

2.4 Summary and conclusion

This thesis focuses on the evaluation of medical services and health care programs using German claims data. Different challenges of claims data studies and methodological approaches are depicted, and the implementation is demonstrated in three exemplary papers. For all three papers, the structure of the claims data allowed us to answer the research questions and implement appropriate study designs. However, German health insurance claims data are still connected with crucial limitations for the estimation of treatment effects. In particular, missing information on confounding and outcome measures such as clinical parameters or patient-reported outcomes represent essential limitations. This minimizes the relevance and impact that claims data studies have to support stakeholder decision-making, where unbiased and trustworthy results are needed. However, current developments to increase relevant information via data linkage and improve the validity of health insurance claims data are important and will increase future use and relevance to stakeholder decision-making.

3. Paper I

Marijic P, Murawski M, Maier W, Hamacher K, Laub O, Lang M, et al. Cost effects of a health coaching in children and adolescents with mental health and developmental disorders. Acad Pediatr. 2021.

DOI: 10.1016/j.acap.2021.12.026

4. Paper II

Marijic P, Schwarzkopf L, Maier W, Trudzinski F, Schwettmann L, Kreuter M. Effects of Influenza Vaccination in Patients with Interstitial Lung Diseases: An Epidemiological Claims Data Analysis. Ann Am Thorac Soc. 2022.

DOI: 10.1513/AnnalsATS.202112-1359OC

5. Paper III

Marijic P, Schwarzkopf L, Schwettmann L, Ruhnke T, Trudzinski F, Kreuter M. Pirfenidone vs. nintedanib in patients with idiopathic pulmonary fibrosis: a retrospective cohort study. Respir Res. 2021;22(1):268.

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