GKV-Routinedatenanalysen zur Unterstützung des Market Access von Arzneimitteln, Impfstoffen und Medizintechnik

Empirische Beispiele zur Machbarkeit

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Zusammenfassung

Im Verlauf des Market Access Prozesses sehen sich die Hersteller von Arzneimitteln, Impfstoffen und Medizintechnik mit einer Vielzahl von Fragestellungen konfrontiert. Diese umfassen bspw. solche über ungedeckte medizinische Bedarfe, zur Epidemiologie von Erkrankungen und der Versorgungssituation von Patienten. Sie betreffen Krankheitskosten, die Effektivität und Sicherheit von Wirkstoffen bzw. Medizintechnik in der realen Versorgungssituation und die Positionierung der eigenen Produkte gegenüber Wettbewerbern.

Auf Abrechnungsdaten der Gesetzlichen Krankenversicherung (sog. GKV-Routinedaten) basierende Studien haben seit Jahren ihren festen Platz in der nationalen und internationalen Versorgungsforschung. Sie liefern einen wichtigen Beitrag zum Verständnis der Versorgungssituation von Patienten in unterschiedlichsten Indikationen, von häufigen Erkrankungen, welche breite Teile der Bevölkerung betreffen bis hin zu seltenen Erkrankungen mit geringen Fallzahlen.

Die vorliegende kumulative Dissertation untersucht anhand von elf ausgewählten empirischen Beispielen das Potential von GKV-Routinedaten-basierten Versorgungsforschungsstudien, den Market Access von Arzneimitteln, Impfstoffen und Medizintechnik aus Perspektive der jeweiligen Hersteller zu unterstützen.

Anhand von sechs Modulen werden Fragestellungen des Market Access von Arzneimitteln beantwortet. Drei dieser Module untersuchen Aspekte der seltenen Erkrankungen Non-CF-Bronchiektasen (NCFB) und Phenylketonurie (PKU). Sie erheben neben Kennzahlen der Epidemiologie ergänzend Krankheitskosten sowie die Last durch Begleiterkrankungen, Arzneimitteltherapien und Hospitalisierungen. Zwei weitere Module betreffen die Indikation Asthma bronchiale. Sie thematisieren die Identifikation der Krankheitsschwere und analysieren die Kosten der Erkrankung diesbezüglich, sowie hinsichtlich Alters- und Geschlechtsunterschieden. Ein nächstes Modul untersucht die Auswirkungen und Kosten von Eisenmangel bei Patienten mit Herzinsuffizienz und vergleicht verschiedene Behandlungsalternativen hinsichtlich Krankheitskosten und Effektivität. Vier Module zeigen Studien aus dem Bereich des Market Access von Impfstoffen. In drei Studien werden die Effekte von aktualisierten Empfehlungen der Ständigen Impfkommission (STIKO) am Beispiel der Pneumokokken-Schutzimpfung untersucht. Eine Studie analysiert die Pneumonie-Erkrankungsrate in verschiedenen Risi-

kopopulationen. Zwei Studien vergleichen die Impfquote und Impfadhärenz von „reifgeborenen“ und „frühgeborenen“ Säuglingen vor und nach der Änderung der Impfempfehlung. Ein weiteres Modul beschreibt die Krankheitslast von HPV-assoziierten anogenitalen Erkrankungen bei jungen Frauen. Abschließend erhebt ein Modul die Kosten und Ressourcenverbräuche von Wirbelsäulenoperationen sowie möglichen Folgeoperationen – eine Studie zur Unterstützung des Market Access von Medizintechnik.

Im Rahmen der vorliegenden kumulativen Dissertation konnte anhand von elf empirischen Beispielen gezeigt werden, dass GKV-Routinedaten-basierte Versorgungsforschungsstudien für Hersteller von Arzneimitteln, Impfstoffen und Medizintechnik ein geeignetes Instrument zur Unterstützung des Market Access ihrer Produkte darstellen können.

Schlagworte

GKV-Routinedaten, Sekundärdaten, Arzneimittel, Impfstoffe, Medizintechnik, Market Access, Gesundheitsökonomie, Versorgungsforschung

Abstract

As part of the market access process, manufacturers of drugs, vaccines and medical technology are confronted with a variety of research questions. These include, for example, questions about unmet medical needs, the epidemiology of diseases and the care situation of patients. They concern medical costs, the effectiveness and safety of products in the real-life healthcare situation, and the positioning of the company's own products compared to competitors. Studies based on statutory health insurance (SHI) claims data have had a firm place in national and international health services research for many years. They provide an important contribution to the understanding of the healthcare situation of patients in a wide variety of indications, from common diseases affecting large parts of the population to rare diseases with small sample size.

This cumulative dissertation examines the potential of SHI claims data based health service research studies to support the market access of drugs, vaccines and medical technology from the perspective of the respective manufacturers.

Six modules answer research questions regarding the market access of drugs. Three of these modules examine aspects of the rare diseases non-cystic fibrosis bronchiectasis (NCFB) and phenylketonuria (PKU). In addition to epidemiological data, they collect data on the costs of illness and the burden of concomitant diseases, drug therapies and hospitalizations. Two further modules concern the indication asthma. They thematize the identification of disease severity and analyze the cost of the disease in terms of age and sex differences. A next module examines the effects and costs of iron deficiency in patients with heart failure and compares different treatment alternatives in terms of cost of illness and effectiveness. Four modules present studies from the field of vaccine market access. Three studies examine the effects of updated recommendations of the Standing Committee on Vaccination (STIKO), using pneumococcal vaccination as an example. One study analyzes pneumonia rates in different risk populations. Two studies compare the vaccination rate and vaccination adherence of "mature" and "preterm" infants before and after the change in vaccination recommendation. Another module describes the disease burden of HPV-associated anogenital disease in young women. Finally, one module analyzes the costs and resource utilization of instrumental spinal surgeries and potential reoperations - a study to support the market access of medical technology.

On the basis of eleven empirical examples this cumulative dissertation showed that SHI claims data based health services research studies can represent a meaningful instrument for manufacturers of drugs, vaccines and medical technology to support the market access of their products.

Key words

Statutory health insurance claims data, secondary data, drug, vaccine, medical technology, market access, health economics, health services research

Inhaltsverzeichnis

1. Motivation und Zielsetzung

1.1. Der Market Access Prozess von Arzneimitteln, Impfstoffen und Medizintechnik

Der Begriff *Market Access* (engl. für Marktzugang) beschreibt den Vorgang des Eintretens eines Unternehmens in einen neuen Markt durch den Absatz von Produkten oder Dienstleistungen. Dabei kann es sich sowohl um den Verkauf eines neuen Produktes in einem bestehenden Markt handeln als auch um die Erschließung eines gänzlich neuen Marktes. Im Kontext von Arzneimitteln, Impfstoffen und Medizintechnik wird unter Market Access im engeren Sinne die Zulassung und der Prozess der Erstattung verstanden. Der Begriff Market Access lässt sich nach Tunder [1] aber auch breiter auslegen und umfasst dann zusätzlich die zwei Phasen vor und nach der Zulassung und Erstattung, da auch innerhalb dieser unterstützende Maßnahmen ergriffen werden können. Der Prozess des Market Access gliedert sich somit in drei Phasen. Im Zentrum steht die *Launch* Phase, welche die Zulassung und Erstattung umfasst. Diese wird von einer *Pre-Launch* Phase und einer *Post-Launch* Phase umrahmt. Tunder gliedert diese drei Phasen des Market Access weiter in vier Prozessphasen mit jeweils zwei Aufgabenschwerpunkten auf:

- Market-Finding
- Market-Initiation
- Market-Entry
- Market-Development

Das *Market-Finding* ist in der Pre-Launch Phase angesiedelt und hat die Suche nach einer Therapielücke bzw. die Identifikation eines ungedeckten medizinischen Bedarfs (engl. *unmet need*) zum Inhalt. Hierzu gehört auch die Unterstützung der klinischen Forschung und Entwicklung durch Marktanalysen. [1]

In der Phase *Market-Initiation* steht die Zulassung des neuen Arzneimittels, Impfstoffs oder Medizintechnikprodukts im Vordergrund. Unterstützend sollte in dieser Phase mit einem gezielten Stakeholder Management begonnen werden. In Deutschland gehören hierzu der Gemeinsame Bundesausschuss (G-BA), das Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), die Krankenkassen der gesetzlichen Krankenversicherung (GKV) sowie der privaten Krankenversicherung (PKV), der GKV-Spitzenverband, im Falle von Impfstoffen die Ständigen Impfkommission (STIKO), zudem Ärztenetzwerke und Fachgesellschaften sowie die Patienten. Sie alle haben ihre

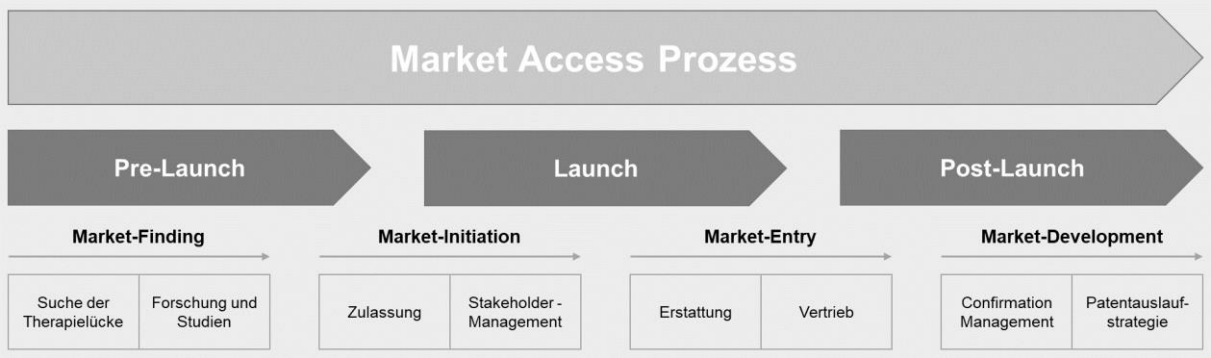
eigene Perspektive und stellen individuelle Ansprüche an die entsprechenden Hersteller. [1]

Anschließend folgt der *Market-Entry*, also der Markteintritt des neuen Arzneimittels, Impfstoffs oder Medizintechnikprodukts [1]. Im Falle von Arzneimitteln beginnt zu diesem Zeitpunkt der AMNOG-Prozess, welcher prüft, inwiefern ein neuer Wirkstoff einen Zusatznutzen gegenüber einer zweckmäßig gewählten Vergleichstherapie aufweist. Der Prozess gliedert sich in mehrere Teilschritte und ist spätestens sechs Monate nach Markteintritt abgeschlossen. [2, 3] Die abschließende Bewertung des neuen Arzneimittels durch den G-BA bildet die Grundlage für die anschließende Preisverhandlung mit dem GKV-Spitzenverband. Der Prozess der Preisverhandlung läuft über einen Zeitraum von sechs Monaten und gliedert sich in mehrere Verhandlungsrunden. Für Arzneimittel, die der G-BA einer Festbetragsgruppe zugeordnet hat, entfällt die Preisverhandlung. Im Rahmen der Preisverhandlung einigen sich der pharmazeutische Unternehmer und der GKV-Spitzenverband auf einen Erstattungsbetrag für das Arzneimittel zu Lasten der GKV. Dieser gilt ab dem 13. Monat nach Markteintritt. Kommt es zu keiner Einigung, werden die offenen Punkte von einer Schiedsstelle innerhalb von drei Monaten bestimmt. [4] Für die Erstattung von Impfstoffen zu Lasten der GKV bedarf es einer Empfehlung der am Robert Koch-Institut (RKI) ansässigen STIKO [5]. Im Bereich der Medizintechnik genehmigt der G-BA im ambulanten Bereich die Erstattung auf Antrag einer unparteiischen Stelle (sog. Verbot mit Erlaubnisvorbehalt) [6]. In der stationären Versorgung gilt die sogenannte Erlaubnis mit Verbotsvorbehalt, welche eine Abrechnung im Rahmen des DRG-Systems ermöglicht [7]. Eine weitere Möglichkeit stellt die 2012 eingeführte Regelung zur Erprobung von Untersuchungs- und Behandlungsmethoden dar [8]. Unmittelbar mit dem Markteintritt beginnt der Vertrieb des Produkts. In dieser Phase des Market Access besteht die Aufgabe in der Generierung und Aufbereitung von Informationen, welche als Argumentationsgrundlage für den Dialog mit Ärzten und Krankenkassen verwendet werden können. [1]

Die abschließende Phase des Market Access bildet das *Market-Development*. Sie ist der Launch Phase nachgelagert und somit Teil des Post-Launches. Das Ziel der pharmazeutischen und Medizintechnik Hersteller ist es hier, den Nutzen ihrer Produkte unter realen Versorgungsbedingungen gegenüber Ärzten und Krankenkassen darzulegen. Dies kann bspw. durch den Nachweis einer erhöhten Adhärenz (Therapietreue

der Patienten) im Vergleich zu einer alternativen Maßnahme gezeigt werden. Die Adhärenz lässt sich unter Umständen durch gezielte *Patient Support Programs* steigern und anhand geeigneter Evaluationen sichtbar machen. Eine weitere Aufgabe sind Maßnahmen der Pharmakovigilanz, also der Dokumentation von Nebenwirkungen und Produktmängeln sowie unerwarteter positiver Effekte. Mit dem Auslauf des Patentschutzes tritt das Produkt in die letzte Phase des Market Access Prozesses ein. Neben spezifischen Strategien zum Umgang mit dem Patentauslauf, lassen sich auch am Ende des Market Access Prozesses unterstützende Maßnahmen denken, die das Produkt bspw. aufgrund von besserer Verträglichkeit (geringerer Nebenwirkungen) oder höherer Therapietreue gegenüber dem Wettbewerb positionieren. [1]

Abbildung 1: Der Market Access Prozess nach Tunder



Quelle: Eigene Darstellung nach Tunder [1].

Abbildung 1 zeigt noch einmal die Prozessabschnitte des Market Access Prozesses. Deutlich wird, dass sich die Hersteller von Arzneimitteln, Impfstoffen und Medizintechnikprodukten in den unterschiedlichen Phasen des Marktzugangs mit einer Vielzahl von Fragestellungen konfrontiert sehen, welche weit über die für die Zulassung und Erstattung notwendigen Informationsbedürfnisse hinausgehen.

1.2. GKV-Routinedaten-basierte Versorgungsforschung

GKV-Routinedaten-basierte Versorgungsforschungsstudien haben in den letzten 15 Jahren in Deutschland beständig zugenommen [9, 10]. Dies ist insbesondere in der relativ zeitnahen und kostengünstigen Verfügbarkeit der Daten begründet, aber auch in der Möglichkeit, große Studienpopulationen in einer sehr detaillierten Datentiefe zu untersuchen [11]. Als GKV-Routinedaten werden im Allgemeinen alle Abrechnungsdaten der Gesetzlichen Krankenversicherung verstanden, die zur Erstattung von Leistungen des Gesundheitswesens dokumentiert werden [10]. Diese können als Sekundärdaten für Forschungszwecke nutzbar gemacht werden [12]. Zu beachten ist, dass diese Daten originär für Abrechnungszwecke erhoben wurden [13]. Angaben zum Versorgungsgeschehen, bestimmte Patientencharakteristika oder auch Behandlungsoutcomes (bspw. die gesundheitsbezogene Lebensqualität) sind nicht oder nur indirekt abgebildet. Beispiele hierfür sind auch die Ergebnisse diagnostischer Tests oder der Schweregrad einer vorliegenden Erkrankung. GKV-Routinedaten enthalten diverse Datenkategorien zu allen Bereichen der Leistungserbringung im Rahmen der GKV [10, 14-16]. Im Folgenden werden die einzelnen Datenkategorien überblicksartig vorgestellt und die wesentlichen Variablen exemplarisch beschrieben.

Die Stammdaten geben Auskunft über demografische Merkmale der Versicherten wie das Geschlecht und das Alter in Form des Geburts- und Sterbedatums. Darüber hinaus finden sich Angaben zur Nationalität, zum Wohnort, Versichertenstatus und der Versichertenzeit sowie der aktuellen Tätigkeit und dem Ausbildungsstand des Versicherten. [10, 14, 17]

Die Daten der ambulanten Versorgung dokumentieren alle Leistungen ambulant tätiger Ärzte der verschiedenen Facharztgruppen. Die erbrachten Leistungen werden mit dem Tag der Leistungserbringung unter Verwendung von EBM (Einheitlicher Bewertungsmaßstab) und OPS (Operationen- und Prozedurenschlüssel) Codes dokumentiert. Die zugehörigen Diagnosen werden in Form von ICD-10-GM (Internationale statistische Klassifikation der Krankheiten und verwandter Gesundheitsprobleme, 10. Revision, German Modification) Codes quartalsweise aggregiert. Die Vergütung der erbrachten Leistungen wird seit 2011 sowohl in Euro Beträgen als auch in Punktwerten dokumentiert. [10, 14, 18]

Im Rahmen der stationären Versorgung werden Diagnosen in Form von Aufnahme, Hauptentlass- und Entlassnebendiagnosen dokumentiert. Angaben über die Dauer der

Hospitalisierung liegen mit dem Beginn und dem Ende der Hospitalisierung exakt vor. Es kann zwischen vorstationär, teilstationär und vollstationären Aufenthalten unterschieden werden. Die Gründe der Hospitalisierung lassen sich in die Kategorien Notfall und geplanter Aufenthalt unterscheiden. Die erbrachten Leistungen werden in Form von OPS Codes dokumentiert. Die der Abrechnung zugrunde liegende Fallpauschale liegt als G-DRG (ab 2020 als aG-DRG) („ausgegliedert“ *German Diagnosis Related Groups*) Code vor, zu der ein individuell abgerechneter Eurobetrag ebenfalls dokumentiert ist. Zudem erfolgt eine zusätzliche Dokumentation im Falle des Versterbens des Patienten. [10, 14, 19]

Die Arzneimitteldaten enthalten alle Verschreibungen, die über eine öffentliche Apotheke abgegeben werden. Dies sind in der Regel alle ambulant verordneten Arzneimittel, zum Teil auch Hilfsmittel. Die jeweiligen Produkte können anhand von PZN (Pharmazentralnummer) Codes eindeutig identifiziert werden. Unter Verwendung der PZN lassen sich Angaben zum Hersteller, Produktname, Wirkstoff, Darreichungsform und Packungsgröße zuspielen. Ferner werden die Facharztgruppe des verordnenden Arztes, das Verordnungsdatum und das Abgabedatum dokumentiert. Die Kosten liegen als Bruttokosten (Apothekenabgabepreis inkl. Rabatte und Patientenzuzahlungen) und aus Perspektive der Krankenkasse (Nettokosten) vor. [10, 14, 20-22]

In den Heilmitteldaten wird die Erbringung und Abrechnung medizinischer Dienstleistungen der Physio- und Ergotherapie, Stimm-, Sprech-, Sprach- und Schlucktherapie sowie Podologie und Maßnahmen der Ernährungstherapie dokumentiert. Die erbrachten Leistungen werden unter anderem mit dem Tag der Leistungserbringung anhand von Heilmittelpositionsnummern dokumentiert und der abgerechnete Eurobetrag übermittelt. [10, 14, 23]

Die Hilfsmitteldaten enthalten die zu Lasten der GKV verordneten Hilfsmittel. Jedes Hilfsmittel wird durch eine Positionsnummer einer Produktgruppe zugeordnet. Ferner ist eine Beschreibung in Form einer Produktbezeichnung verfügbar. Das Datum der Verschreibung und die abgerechneten Kosten in Euro sind ebenfalls dokumentiert. [10, 14]

Die Daten zur Arbeitsunfähigkeit enthalten taggenaue Angaben zu Beginn und Ende der Arbeitsunfähigkeit, sowie die Diagnosen, welche die Arbeitsunfähigkeit bedingen als auch die Facharztgruppe des behandelnden Arztes. Beachtenswert ist hierbei, dass lediglich der Krankenkasse gemeldete Krankentage dokumentiert sind. In Fällen,

bei denen der Arbeitgeber erst am zweiten oder dritten Tag ein ärztliches Attest verlangt, bilden die Daten nicht die gesamten Fehltage ab. [10, 14, 24]

Im Falle andauernder Krankheit (ab der siebten Woche), bilden die Krankengelddaten die Zahlungen des Krankengeldes der Krankenkasse an den Versicherten ab. Dokumentiert werden die Dauer der Zahlungen und die Höhe in Euro. [10, 14]

Die Datenkategorie Rehabilitation enthält Angaben zur medizinischen Rehabilitation, sofern die Krankenkasse für die Erstattung zuständig ist. Dies ist in der Regel der Fall bei Rentnerinnen und Rentnern, nicht erwerbstätigen Erwachsenen sowie bei Kindern und Jugendlichen. Die Daten enthalten die Art der Rehabilitationsmaßnahme, die Dauer und die Kosten in Euro als auch die Diagnose der zugrundeliegenden Erkrankung. [10, 14]

Chronisch kranke Patienten haben die Möglichkeit, an Disease-Management-Programmen teilzunehmen. Im Rahmen der Dokumentation werden detaillierte Daten zur jeweiligen Erkrankung und ihrer Therapie als auch weiterführende Daten zum Patienten, wie Körpergroße, Körpergewicht und Raucherstatus erhoben. Zudem wird die Dauer der Teilnahme am Programm erfasst. [10]

Psychiatrische Institutsambulanzen erbringen alle Leistungen der psychiatrisch-psychotherapeutischen Diagnostik und Therapie. Die Vergütung kann pauschal, nach Komplexleistungen oder auch nach EBM erfolgen. Die verfügbaren Daten der psychiatrische Institutsambulanzen variieren in Abhängigkeit von der jeweiligen Erstattungsform und geben im Fall einer pauschalen Abrechnung nur Angaben zum Rechnungsdatum und der Höhe der Kosten in Euro wieder. [10, 25]

Unter Verwendung von GKV-Routinedaten lassen sich eine Vielzahl von verschiedenen Studientypen realisieren, welche im Bereich der Versorgungsforschung angesiedelt sind, aber auch Bezug zur Epidemiologie haben. Exemplarisch sollen hier vier Typen von Studien vorgestellt werden, welche sich mit den in GKV-Routinedaten enthaltenen Informationen umsetzen lassen:

1. Epidemiologische Studien/Krankheitslast-Analysen (Burden-of-Disease)
2. Krankheitskosten-Analysen (Cost-of-Illness)
3. Evaluation gesundheitspolitischer Interventionen (Policy Implication)
4. Medikamenten-/Interventionsvergleiche (Comparative Effectiveness)

Im Rahmen von *Burden-of-Disease* Studien werden neben den klassischen Kennzahlen der Epidemiologie wie der Prävalenz und der Inzidenz ebenfalls Auswertungen zur Krankheitslast durchgeführt. Die Prävalenz beschreibt die Rate der Erkrankten in einem definierten Zeitraum (Periodenprävalenz) oder zu einem definierten Zeitpunkt (Stichtagsprävalenz). Die Inzidenz beschreibt die Rate der Neuerkrankten in einem definierten Zeitraum. Weitere Beschreibungen der Krankheitslast können bspw. auftretende Komorbiditäten, die Zahl der Arztkontakte und Hospitalisierungen oder auch die Einnahme von Arzneimitteln sein. Des Weiteren können Analysen der Mortalität Bestandteil von Burden-of-Disease Studien sein. In Abhängigkeit von der jeweiligen Fragestellung bieten sich unterschiedliche Studiendesigns zur Beantwortung an [14].

Krankheitskostenanalysen (engl. *Cost-of-Illness*) untersuchen die Kosten, die durch eine spezifische Erkrankung verursacht werden. Sie stellen damit einen Spezialfall der Kostenanalyse dar [26]. Je nach verwendeter Methodik lassen sich die direkten Kosten der Erkrankung ermitteln, ggf. ergänzt um die indirekten Kosten [27-29]. Unter Verwendung von GKV-Routinedaten lassen sich für alle Leistungsbereiche sehr detailliert die Kostentreiber aus Perspektive der GKV ermitteln. Das Ziel von Krankheitskostenanalysen besteht darin, Erkenntnisse über die Höhe und Zusammensetzung der Kosten zu gewinnen, um eine Vergleichbarkeit der ökonomischen Belastung verschiedener Erkrankungen herzustellen, die Identifikation von Kostentreibern sowie die Generierung von Inputvariablen für gesundheitsökonomische Evaluationen bereitzustellen. Diese Maßnahmen verfolgen letztlich das Ziel, eine Entscheidungsgrundlage zu schaffen, um knappe Ressourcen in der Versorgung der Patienten gezielter einsetzen zu können. Dabei spielt nicht nur die Zusammensetzung der Kosten für die jeweilige Erkrankung eine Rolle, sondern auch der Vergleich mit anderen Erkrankungen.

Die Folgen gesundheitspolitischer Entscheidungen im Versorgungsgeschehen können Gegenstand von Evaluationen sein (*Policy Implication studies*) [30]. Bspw. können dies Gesetzesänderungen sein, wie die Einführung der Praxisgebühr von 2004 bis 2012, aber auch Entscheidungen einzelner Akteure im Gesundheitswesen wie Impfempfehlungen der STIKO oder Leitlinienänderungen spezifischer Fachgesellschaften. Ziel ist es dabei jeweils, die Umsetzung der Entscheidung in der Praxis zu überprüfen und die jeweiligen Auswirkungen auf die mitunter veränderte Versorgung zu bewerten.

Vergleiche von Interventionen im Allgemeinen und von Arzneimitteln im Speziellen lassen sich unter dem englischen Begriff der *Comparative Effectiveness* zusammenfassen. Ähnlich mehrarmigen klinischen Studien vergleichen diese Analysen zwei oder mehr Behandlungsalternativen miteinander. Im Unterschied zu klinischen Studien und ihrem kontrollierten Setting findet der Vergleich im Rahmen von Versorgungsforschungsstudien unter realen Versorgungsverhältnissen statt. Betrachtet werden dabei auch Patienten, die die engen Einschlusskriterien einer klinischen Studie nicht erfüllen, wie auch breitere Behandlungsansätze auf Seiten der Leistungserbringer. [31-33] Ziel dieses Studientyps ist es, jeweils zu untersuchen, wie sich die unterschiedlichen Interventionen im Vergleich zueinander bezogen auf ein Behandlungsziel darstellen. Bspw. kann untersucht werden, ob ein Arzneimittel im Vergleich zu einem anderen über einen definierten Zeitraum zu weniger Arztkontakten aufgrund von Nebenwirkungen führt und somit eine höhere Verträglichkeit für die Patienten aufweist.

1.3. Ziel der Dissertation

Das Ziel der vorliegenden Dissertation ist die Untersuchung des Potentials von GKV-Routinedaten-basierten Versorgungsforschungsstudien zur Unterstützung des Market Access von Arzneimitteln, Impfstoffen und Medizintechnikprodukten aus Perspektive der jeweiligen Hersteller.

2. Beitrag der vorliegenden kumulativen Dissertation

Die vorliegende kumulative Dissertation untersucht anhand von elf ausgewählten empirischen Beispielen, welchen Beitrag GKV-Routinedaten-basierte Versorgungsforschung im Rahmen des Market Access Prozesses von Arzneimitteln, Impfstoffen und Medizintechnikprodukten leisten kann. Die einzelnen Module zeigen Versorgungsforschungsstudien, die im Auftrag eines pharmazeutischen bzw. Medizintechnik Herstellers durchgeführt wurden. Im Folgenden werden die einzelnen Module thematisch nach den zugrunde liegenden Produkten (Arzneimitteln, Impfstoffen und Medizintechnik) sortiert und im zeitlichen Ablauf des Market Access Prozesses angeordnet vorgestellt. Die Einordnung erfolgt dabei dem breiten Ansatz nach Tunder [1] folgend in die drei Phasen Pre-Launch, Launch und Post-Launch. Von einer weiteren Aufgliederung in die vier Prozessphasen und die damit verbundenen acht Aufgabenfelder soll an dieser Stelle abgesehen werden, da eine Abgrenzung der Module nicht hinreichend möglich und für die Beantwortung der Studienfrage dieser Dissertation nicht nötig ist. Ferner wird auf den jeweiligen Studientyp, die Forschungsfrage, die verwendete Methodik sowie die Studienergebnisse eingegangen. Bezug genommen wird dabei auch auf die Bedeutung der Ergebnisse und die mögliche weitere Nutzung dieser im Rahmen des Market Access Prozesses.

2.1. Arzneimittel

Bei den Modulen 1 bis 6 handelt es sich um Versorgungsforschungsstudien zur Unterstützung des Market Access von Arzneimitteln. Fünf Module sind Beispiele angewandter GKV-Routinedatenanalysen. Ein Modul (Modul 5) zeigt anhand eines systematischen Literaturreviews Möglichkeiten zur Unterstützung von Studienvorhaben auf.

Die in **Modul 1** *"Incidence of patients with non-cystic fibrosis bronchiectasis in Germany – A healthcare insurance claims data analysis"* durchgeführte Studie stellt ein Beispiel für eine Krankheitslast-Analyse in der Indikation Non-CF-Bronchiektasen (NCFB) dar, eine seltene Variante der Bronchiektasie, die nicht durch eine Mukoviszidose verursacht wird. Im Rahmen der Analyse sollte die epidemiologische Kennzahl der Inzidenz ermittelt werden. Sie beschreibt den Anteil der Patienten, die jährlich neu an NCFB erkranken. Die Ermittlung der Inzidenz einer Erkrankung mithilfe von GKV-Routinedaten stellt eine methodische Herausforderung dar. Aufgrund des verfügbaren Datenzeitraums von in der Regel sechs Jahren, kann nicht ausgeschlossen werden, dass Patienten bereits vor diesem Zeitraum erkrankt sind. Dies führt gegebenenfalls

zu einer Überschätzung der Inzidenz, wie Abbas et al. zeigen konnten und muss bei der Interpretation der Analyseergebnisse beachtet werden [34]. Ferner sollte die Population der neuerkrankten NCFB Patienten charakterisiert und ihre Krankheitslast im Jahr der Diagnosestellung anhand von Begleiterkrankungen und der Inanspruchnahme des Gesundheitssystems quantifiziert werden. Zur Ermittlung der Inzidenz konnte ein Zeitraum von vier Datenjahren herangezogen werden. Dabei wurden die ersten drei Datenjahre als Vorbeobachtungszeitraum verwendet und das letzte Datenjahr als Jahr der Inzidenzmessung. Patienten galten als neuerkrankt, wenn sie im Jahr der Inzidenzmessung mit NCFB diagnostiziert wurden und in den drei vorherigen Datenjahren keine NCFB Diagnosen aufwiesen. Die Population wurde anhand von Alter und Geschlecht charakterisiert. Unter Verwendung von ICD-10-GM Codes wurden die häufigsten Begleiterkrankungen ermittelt. Mit Hilfe von Verschreibungsdaten konnte der Anteil der Patienten bestimmt werden, welcher mit Antibiotika therapiert werden musste. Zudem wurde der Anteil an diesen Patienten ermittelt, die im Jahr der Erstdiagnose aufgrund von NCFB hospitalisiert werden mussten.

Im Rahmen der vorliegenden Studie wird die Inzidenz von NCFB in Deutschland mit 21,6 Patienten pro 100.000 Einwohner ermittelt. 98,4 % der NCFB Patienten erhalten ihre Erstdiagnose im Erwachsenenalter. Die Geschlechterverteilung zeigt einen höheren Anteil an Männern mit 52,7 %. Die Patienten weisen häufig weitere Atemwegserkrankungen wie COPD (41,3 %) und Asthma (32,8 %) auf. Im Jahr der Erstdiagnose werden 54,6 % der NCFB Patienten mit Antibiotika therapiert und acht Prozent dieser Patienten werden aufgrund von NCFB zudem hospitalisiert.

Die Studie wurde in der Pre-Launch Phase des Market Access Prozesses durchgeführt. Die gewonnenen Erkenntnisse ließen sich aber auch während der Launch Phase – in welcher aktuelle Zahlen zur Inzidenz und Prävalenz im Rahmen des AMNOG Prozesses gefordert sind [35] – sowie in der Post-Launch Phase zur Interaktion mit Ärzten und Krankenkassen verwenden, um die Bedeutung der Erkrankung zu verdeutlichen. Zur Unterstützung des Market Access quantifiziert **Modul 1** die Anzahl der Neuerkrankten mit NCFB in Deutschland und bestätigt damit die Seltenheit der Erkrankung. Weiterhin gibt die Studie Einblicke in die aktuelle Versorgungssituation der Patienten und beschreibt das Ausmaß des unmet need der Patienten, die aufgrund von NCFB hospitalisiert werden.

In den **Modulen 2 und 3** *“Clinical burden of illness in patients with phenylketonuria (PKU) and associated comorbidities - a retrospective study of German health insurance claims data”* und *“Health economic burden of patients with phenylketonuria (PKU) – A retrospective study of German health insurance claims data”* werden die Prävalenz, Krankheitslast sowie die Krankheitskosten für an Phenylketonurie (PKU) erkrankten Patienten untersucht. Hier konnte für eine weitere seltene Erkrankung das Potential von GKV-Routinedaten genutzt werden. Aufgrund der Größe der verfügbaren Datensätze, lassen sich in der Regel ausreichend viele Patienten in die Studienpopulation einschließen, um statistisch belastbare Ergebnisse zu generieren [14-16]. Der Vergleich mit einer alters- und geschlechtsadjustierten Gruppe von nicht an PKU erkrankten Versicherten ermöglichte es, die häufigsten Begleiterkrankungen und Arzneimittelverschreibungen zu bestimmen, welche verhältnismäßig häufiger mit PKU in Verbindung stehen. Ferner ermöglichte der Gruppenvergleich die Quantifizierung der PKU-spezifischen Krankheitskosten. Zudem wurde eine Subgruppenanalyse durchgeführt, in der die prävalenten PKU Patienten anhand ihres Geburtsjahres in zwei Gruppen unterteilt wurden. PKU Patienten, die vor der Einführung des PKU Neugeborenen Screenings in Deutschland im Jahre 1969/70 geboren wurden und solche, die erst nach Einführung der Maßnahme geboren wurden. Die in **Modul 2** vorgestellte Studie liefert aktuelle Daten zur Prävalenz (10,1 pro 100.000 Menschen) und Krankheitslast von PKU, welche sich durch ein erhöhtes Risiko für Begleiterkrankungen bemerkbar macht. Die Studie bestätigt dabei bereits bekannte Begleiterkrankungen wie Depressionen, kann aber auch ein erhöhtes Risiko für ischämische Herzkrankheit zeigen. Dieses erhöhte Risiko spiegelt sich auch in verhältnismäßig höheren Verschreibungsraten für die entsprechenden Medikamente wider. In **Modul 3** werden die PKU spezifischen Krankheitskosten quantifiziert. Sie übertreffen die Kosten der Vergleichsgruppe um den Faktor 2,26. Dies wird insbesondere durch einen kostenintensiven Medikamentenbedarf als auch durch höhere Kosten der ambulanten und stationären Versorgung erklärt. Der Unterschied fällt für frühzeitig diagnostizierte Patienten noch deutlicher aus. Sie verursachen im Schnitt fast viermal so hohe Kosten, wie ihre Kontrollen (Faktor 3,96).

Die in den **Modulen 2 und 3** vorgestellten Studien wurden als ein zusammenhängendes Forschungsvorhaben in der Post-Launch Phase durchgeführt. Die gewonnenen Erkenntnisse zur Prävalenz, Krankheitslast und den Krankheitskosten von PKU könnten aber auch in der Pre-Launch und der Launch Phase unterstützend wirken, wie

bereits für **Modul 1** beschrieben. Zur Unterstützung des Market Access stellen beiden Studien aktuelle Daten bereit. Sie unterstreichen die Seltenheit der Erkrankung und den therapeutischen Bedarf der Patienten und bieten einen Ausgangspunkt zum Dialog mit Ärzten und Krankenkassen.

Die in **Modul 4** *„Healthcare costs and resource utilization of asthma in Germany: a claims data analysis"* präsentierte Studie untersucht die Krankheitskosten sowie die zugrundeliegende Ressourceninanspruchnahme von Patienten mit Asthma bronchiale. Unter Verwendung einer Kontrollgruppe wurden die spezifischen Krankheitskosten von Asthma bronchiale bestimmt und die Inanspruchnahme ambulanter und stationärer Versorgung, als auch die medikamentöse Therapie untersucht. Ebenso wie in den **Modulen 2 und 3** wurde eine alters- und geschlechtsadjustierte Kontrollgruppe verwendet. Die so ermittelten Kostenunterschiede wurden nach Altersgruppen sowie für Männer und Frauen getrennt aufgeschlüsselt. In einem weiteren Schritt konnte anhand der verschriebenen Asthmamedikation eine Unterscheidung in intermittierendes und persistierendes Asthma bronchiale vorgenommen werden. Auf diese Weise zeigt die Studie ein sehr detailliertes Bild der finanziellen Belastung durch die Erkrankung aus Perspektive der für die Erstattung zuständigen Krankenkassen. Die spezifischen jährlichen Krankheitskosten von Asthma bronchiale bewegen sich dabei zwischen 107 € in der Gruppe der 6-18-jährigen Frauen mit intermittierendem Asthma bronchiale und 1.208 € in der Gruppe der erwachsenen Frauen mit persistentem Asthma bronchiale. Durchschnittlich liegen die spezifischen jährlichen Krankheitskosten bei 753 €. Dieser Kostenunterschied zeigt sich auch in einer höheren Anzahl von ambulanten Arztbesuchen, Hospitalisierungen und Verschreibungen.

Einordnen lässt sich **Modul 4** sowohl in die Pre-Launch als auch in die Post-Launch Phase des Market Access Prozesses. Die in **Modul 4** vorgestellte Studie wurde zu einem Zeitpunkt durchgeführt, als der beauftragende pharmazeutische Hersteller bereits mehrere Produkte zur Behandlung von Asthma bronchiale anbot und zeitgleich an neuen Wirkstoffen forschte. Die Forschungsergebnisse der Studie verdeutlichen die gesundheitsökonomische Bedeutung dieser vergleichsweise häufigen Erkrankung. Zudem erlaubt die Einteilung in Krankheitsschwere, Altersgruppen und Geschlecht eine sehr detaillierte Aufschlüsselung der spezifischen Krankheitskosten. Wie bei den zuvor vorgestellten Modulen ausgeführt, lassen sich die generierten Ergebnisse als Grundlage für den Dialog mit Ärzten und Krankenkassen verwenden.

Modul 5 *„Assessing asthma severity based on claims data: a systematic review"* stellt eine Ergänzung zu der in **Modul 4** beschriebenen Versorgungsforschungsstudie dar. Mangels vorhandener internationaler Standards zur Bestimmung der Schwere von Asthma bronchiale mit den in GKV-Routinedaten vorhandenen Informationen, haben sich in der Praxis diverse Ansätze entwickelt. In **Modul 5** wurde ein systematisches Review der internationalen Literatur durchgeführt, um für die Erkrankung Asthma bronchiale, Algorithmen zur Einteilung des Krankheitsschweregrads mithilfe von Abrechnungsdaten der Krankenversicherung zu identifizieren und die Übertragbarkeit auf deutsche GKV-Routinedaten zu prüfen.

Die Arbeit zeigt, dass der überwiegende Teil der identifizierten Studien zwar einen bereits vordefinierten und in der Literatur etablierten Algorithmus verwendet, neuere Studien aber zunehmend eigene Definitionen der Krankheitsschwere entwickeln. Je nach Fragestellung können Erkrankte in Patienten mit leichtem, leichtem intermittierenden, intermittierenden, moderatem, persistierenden, leicht persistierendem, moderat persistierendem, schwer persistierendem, schwerem, geringen Risiko und hohem Risiko Asthma bronchiale eingeteilt werden. Eine Übertragbarkeit auf deutsche GKV-Routinedaten ist aufgrund der Datenstruktur nicht vollständig möglich und muss bei der Adaption entsprechend berücksichtigt werden. Die in **Modul 5** vorgestellte Studie bietet eine Übersicht zur Verbreitung und Akzeptanz von Algorithmen zur Einteilung des Krankheitsschweregrads von Asthma bronchiale auf Basis von Abrechnungsdaten der Krankenkassen. Sofern es für die jeweilige Fragestellung sinnvoll ist, kann auf die in der Literatur bereits etablierten Algorithmen zugegriffen werden. Fragestellungen, die eine abweichende Einteilung der Krankheitsschwere erfordern, können gegebenenfalls auf die weiteren vorgestellten Studien zurückgreifen, bzw. auf diese aufbauen. Wie schon **Modul 4** kann die Studie keiner einzelnen Phase des Market Access Prozesses eindeutig zugeordnet werden. Es handelt sich um eine indirekt unterstützende Studie, deren Ergebnisse bei der Entwicklung von Studiendesigns berücksichtigt werden können, sofern eine Einteilung der Patienten in spezifische Schweregrade des Asthma bronchiale notwendig ist.

Die letzte im Bereich der Arzneimittel vorgestellte Studie ist das **Modul 6** *"Retrospective analysis into differences in heart failure patients with and without iron deficiency or anaemia"* in der zum einen die Auswirkungen von Begleiterkrankungen auf eine zuvor

gewählte Haupterkrankung untersucht werden (Krankheitslast- und Krankheitskostenanalyse) als auch ein Vergleich verschiedener Behandlungsalternativen vorgenommen wird (Comparative Effectiveness). Patienten mit Herzinsuffizienz wurden anhand von ICD-10-GM Diagnose Codes und Medikamentenverschreibungen in Herzinsuffizienz Patienten mit und ohne Eisenmangel bzw. Eisenmangelanämie eingeteilt. Mithilfe eines Kontrollgruppendesigns wurde im ersten Studienteil der Einfluss eines unbehandelten Eisenmangels auf die verursachten Ressourcenverbräuche, Krankheitskosten und Mortalität der Herzinsuffizienzpatienten quantifiziert. Im zweiten Teil der Studie wurden verschiedene Therapiealternativen des Eisenmangels bzw. der Eisenmangelanämie untersucht. Die Vergleichsgruppen wurden nach Alter und Geschlecht sowie nach dem Schweregrad der Herzinsuffizienz ausgeglichen. Die Paare wurden zudem so gewählt, dass sie möglichst gleich hohe Kosten im Vorbeobachtungszeitraum aufwiesen, um für nicht beobachtbare Einflüsse auf den Gesundheitszustand der Patienten auszugleichen. Um die Auswirkungen verschiedener Behandlungsalternativen zu untersuchen, wurden im zweiten Studienteil die Patienten mit Herzinsuffizienz und einem Eisenmangel bzw. Eisenmangelanämie in drei Vergleichsgruppen eingeteilt. Die erste Gruppe bestand aus Patienten, für die keine Therapie ihres Eisenmangels zu Lasten der GKV dokumentiert wurde. Die zweite Gruppe umfasste Patienten, deren Eisenmangel mit oral eingenommenen Eisenpräparaten therapiert wurde. Die dritte Gruppe bildeten Patienten, welche zur Therapie ihres Eisenmangels bzw. ihrer Eisenmangelanämie mit intravenös verabreichten Eisenpräparaten behandelt wurden. Im Rahmen der Studie kann gezeigt werden, dass Herzinsuffizienzpatienten mit einem unbehandelten Eisenmangel jährlich zusätzliche Kosten in Höhe von 849 € verursachen, signifikant häufiger hospitalisiert werden müssen (72.9 % vs. 50.5 %) und zudem eine höhere Mortalität als Herzinsuffizienzpatienten ohne Eisenmangel bzw. Eisenmangelanämie (33.1 % vs. 24.1 %) aufweisen. Der Vergleich der Behandlungsalternativen zeigt eine verringerte Mortalität, wenn der Eisenmangel bzw. die Eisenmangelanämie oral bzw. intravenös behandelt wird (23,6 % (keine Behandlung) vs. 22,4 % (orale Eisengabe) vs. 18,5 % intravenöse Eisengabe)), wobei der Vorteil bei den intravenösen Präparaten etwas deutlicher ausfällt. Die Studie wurde in der Post-Launch Phase des Market Access Prozesses durchgeführt. Mit ihr gelang es, die Auswirkungen eines zusätzlich auftretenden Eisenmangels bzw. einer Eisenmangelanämie auf Patienten mit Herzinsuffizienz für die Bereiche Krankheitskosten, Krankheitslast und Mortalität zu quantifizieren. Der Vergleich der Behandlungsalternativen unterstrich den

Bedarf einer Therapie des Eisenmangels bzw. der Eisenmangelanämie. Zur Unterstützung des Market Access können die Ergebnisse verwendet werden, um sowohl betroffene Patienten als auch behandelnde Ärzte für die Vorteile eine Eisenmangeltherapie zu sensibilisieren.

2.2. Impfstoffe

In den **Modulen 7 bis 10** werden empirische Beispiele für GKV-Routinedaten-basierte Versorgungsforschungsstudien vorgestellt, die zur Unterstützung von Impfstoffen im Rahmen des Market Access durchgeführt wurden.

In der in **Modul 7** *„Burden of HPV related anogenital diseases in young women in Germany – an analysis of German statutory health insurance claims data from 2012 to 2017"* vorgestellten Studie sollte die Krankheitslast für verschiedene Gruppen von den Anus als auch die Genitalien betreffende (anogenitalen) Erkrankungen, welche durch eine humane Papillomaviren (HPV) Infektion verursacht werden können, bestimmt werden. Anhand von vier Geburtsjahrgängen sollte die Entwicklung der Prävalenz der eingeschlossenen Erkrankungen bei jungen Frauen nachgezeichnet werden. Die Studienpopulation wurde dabei so gewählt, dass es sich um die vier ersten Jahrgänge handelte, die von der Impfempfehlung der STIKO zur HPV-Vakzination profitieren konnten. Anhand von ICD-10-GM Codes wurden HPV-assoziierte anogenitale Erkrankungen in den GKV-Routinedaten identifiziert und in Erkrankungsgruppen unterteilt. Die Studie zeigt einen statistisch signifikanten Rückgang der Prävalenz von Genitalwarzen und anogenitale Erkrankungen der Krankheitsstufe 3 nach Aussprache der Impfempfehlung für die HPV-Impfung durch die STIKO. Die Prävalenz von anogenitale Erkrankungen der Krankheitsstufen 1 und 2 verblieb auf einem gleichbleibenden Niveau.

Die Studie wurde in der Post-Launch Phase durchgeführt und leistet zur Unterstützung des Market Access einen Beitrag durch die Quantifizierung der Krankheitslast von anogenitalen Erkrankungen bei jungen Frauen. Inwiefern der oben genannte Rückgang einzelner Krankheitsstufen in direktem Zusammenhang mit der HPV-Impfung steht, konnte im Rahmen der Analyse nicht untersucht werden, da der Impfstatus der Studienpopulation in der verwendeten Datengrundlage nicht verfügbar ist. Hier muss auf ergänzende Untersuchungen zurückgegriffen werden, welche die Impfquote der entsprechenden Jahrgänge erhoben haben. Im Zusammenspiel mit der ergänzenden Literatur kann die Studie als Argumentationsgrundlage zugunsten von HPV-Impfungen

dienen. Theoretisch ließe sich diese Studie auch in den beiden früheren Phasen des Market Access Prozesses zur Unterstützung des eigenen Impfstoffes, welcher sich dann noch in der Entwicklung bzw. Zulassung befände, durchführen. Dies würde aber das Vorhandensein eines Wettbewerberproduktes im Markt erfordern. Die veröffentlichten Studienergebnisse könnten dann ebenfalls vom Wettbewerber genutzt werden, um seine Marktposition zu sichern. Daher ist es unwahrscheinlich, dass diese Form der Studie in der Pre-Launch oder Launch Phase des eigenen Impfstoffes durchgeführt würde.

In **Modul 8** *"Rates of pneumonia among children and adults with chronic medical conditions in Germany"* sollte für den Zeitraum nach der Empfehlung der STIKO zur generellen Impfung aller Kinder (in den ersten zwei Lebensjahren) gegen Pneumokokken [36] die Erkrankungsrate an Pneumonien ermittelt werden. Die Studienpopulation wurde anhand von Begleiterkrankungen in drei Risikogruppen unterteilt: Patienten ohne erhöhtes Risiko einer Pneumonie, Patienten mit erhöhtem Risiko und Patienten mit einem sehr hohen Risiko. So wurden bspw. Patienten mit HIV, chronischen Nierenerkrankungen oder bösartigen Neubildungen als Hochrisikopatienten betrachtet. Des Weiteren wurde die Studienpopulation in Altersgruppen von <5 Jahren, 5-17 Jahren, 18-49 Jahren, 50-59 Jahren und ≥60 Jahren eingeteilt. Der gewählte Analysezeitraum (2009-2012) beginnt zweieinhalb Jahre nach der Empfehlung der STIKO. Im Rahmen der Studie kann für Patienten mit erhöhtem Risiko eine 1,7-fach bis 2,5-fach (<5-Jährige bzw. ≥60-Jährige) höhere Pneumonie-Rate im Vergleich zu Patienten ohne erhöhtem Risiko gezeigt werden. Für Patienten mit einem sehr hohen Risiko ist die Rate um das 1,8-fache bis 4,1-fache (<5-Jährige bzw. ≥60-Jährige) erhöht. Zudem zeigt sich, dass das Risiko für eine Pneumonie mit der Zunahme der Risikofaktoren (engl. *risk stacking*) steigt.

Die Studie wurde in der Post-Launch Phase durchgeführt. Sie quantifiziert die besondere Krankheitslast einzelner Patientengruppen. Die Studienergebnisse können als Argumentationsgrundlage für den erhöhten Präventionsbedarf dieser Gruppen dienen bspw. in Form einer Ausweitung der Durchimpfung dieser Risikogruppen. Wie bereits bei **Modul 7** angemerkt, ist es denkbar, diese Studie in jeder Phase des Market Access Prozesses durchzuführen. Sofern eine Veröffentlichung der Ergebnisse angestrebt wird, ist ein solches Vorgehen in der Pre-Launch oder Launch-Phase des eigenen Produktes jedoch unwahrscheinlich.

Das **Modul 9** *„Vaccination rates and adherence in pneumococcal conjugate vaccination in mature born infants before and after vaccination schedule change - A claims database analysis"* und das **Modul 10** *„Vaccination rates and adherence in premature infants before and after pneumococcal conjugate vaccine schedule change for term infants – A claims data-base analysis in Germany"* analysieren die Auswirkung einer gesundheitspolitischen Entscheidung auf das Verhalten der Versicherten. Im August 2015 hat die STIKO ihre Empfehlung zum Impfschema der Pneumokokken-Schutzimpfung für Neugeborene aktualisiert [37]. Die Änderung sieht eine Reduktion der Impfdosen von vier auf drei Dosen für „reifgeborene Säuglinge" vor. Entfallen ist die Impfdosis im Alter von 3 Monaten als Teil der Grundimmunisierung. Für „frühgeborene Säuglinge" bleibt das Impfschema unverändert. Sie sollen weiterhin vier Impfdosen erhalten, die aus drei Impfdosen zur Grundimmunisierung und einer Booster-Impfdosis bestehen. Die beiden Studien sollten untersuchen, welche Auswirkungen die Änderung des Impfschemas auf die Rate der vollständig geimpften Neugeborenen hat und ob die zeitliche Abfolge der empfohlenen Impftermine eingehalten wurde (Adhärenz). **Modul 9** untersucht die Studienpopulation der „reifgeborenen" Kinder und **Modul 10** die der „frühgeborenen" Kinder. Als Vergleichsgruppe zur Messung der Auswirkungen der Änderung des Impfschemas diente jeweils eine Geburtskohorte aus der Zeit vor der Anpassung der Empfehlung (Geburtskohorte 2013), sowie die hexavalente Schutzimpfung gegen Kinderlähmung, Diphtherie, Tetanus, Keuchhusten, Haemophilus influenzae Typ b und Hepatitis B. Auf diese Weise sollte für generelle Änderungen der Impfakzeptanz im Zeitverlauf kontrolliert werden. Der Beobachtungszeitraum umfasste die individuellen 24 Monate nach Geburt des jeweiligen Kindes.

Für „reifgeborene" Kinder zeigt **Modul 9** eine leichte Zunahme des Anteils der Kinder mit einer vollständigen Impfserie nach der Änderung des Impfschemas (75,6 % zu vormals 67,7 %), wobei 3,9 % weiterhin nach dem alten Impfschema mit vier Impfdosen geimpft wurden. Im Gegensatz dazu zeigt **Modul 10** eine deutliche Reduktion des Anteils der Kinder mit einer vollständigen Impfserie für „frühgeborene" Kinder (von 65,4 % auf 40,8 %). Interessanterweise wurde für die Vergleichsimpfung mit der hexavalenten Schutzimpfung nahezu keine Veränderung der Durchimpfung der Kinder beobachtet. Lediglich der Anteil der ungeimpften Kinder reduzierte sich signifikant (von 7,9 % auf 5,4 %). Für die Pneumokokken-Schutzimpfung blieb der Anteil der ungeimpften Kinder sowohl für „reifgeborene" Kinder als auch für „frühgeborene" Kinder konstant. Die Analyse der Adhärenz zeigt eine Zunahme bei der ersten Impfdosis bei

den „reifgeborenen“ Kindern (**Modul 9**) von 44,2 % auf 51,1 %, eine Abnahme um 6,5 %-Punkte bei der zweiten Dosis und eine leichte Zunahme bei der Booster-Impfdosis von 45,1 % auf 46,3 %. Für „frühgeborene“ Kinder (**Modul 10**) zeigt sich die gleiche Entwicklung mit einer Verbesserung der Adhärenz bei der ersten Dosis (von 40,5 % auf 44,8 %), einer Abnahme bei der zweiten und dritten Dosis (9,5 %-Punkte und 5,8 %-Punkte weniger) und einer leichten Zunahme bei der Booster-Impfdosis von 44,4 % auf 47,6 %.

Beide Studien wurden in der Post-Launch Phase durchgeführt und liefern dem Impfstoffhersteller eine Reihe von Anknüpfungspunkten zum Austausch mit den relevanten Entscheidern (z.B. STIKO) und impfenden Kinderärzten. Als erstes ist hier der Rückgang der vollständig immunisierten „frühgeborenen“ Kinder zu nennen, welcher dem Anschein nach mit der Änderung der Impfempfehlung für „reifgeborene“ Kinder in Zusammenhang steht. Für den Impfstoffhersteller bedeutet dies einen Rückgang des eigenen Absatzes und für die betroffenen Kinder ein potentiell verringertes Schutzniveau [37]. Als zweites zeigen die Ergebnisse der Adhärenz Analyse eine Unterversorgung sowohl für „reifgeborene“ als auch für „frühgeborene“ Kinder auf. Unter der Annahme, dass eine strikte Einhaltung der Impftermine, einen optimalen Infektionsschutz ermöglicht, verdeutlichen die beiden Studien, dass mehr als die Hälfte der betrachteten Kinder nicht optimal geschützt sind. Drittens bietet die Studie eine Diskussionsgrundlage zur Frage, ob und wie der über die Zeit konstant bleibende Anteil nicht geimpfter Kinder (8,8-9,1 % „reifgeborene“ bzw. 5,8-5,9 % „frühgeborene“ Kinder) gesenkt werden sollte.

2.3. Medizintechnik

In **Modul 11** *“Burden of disease of reoperations in instrumental spinal surgeries in Germany”* wurden eine Krankheitslast- und eine Krankheitskosten-Analyse im Rahmen einer GKV-Routinedaten-basierten Versorgungsforschungsstudie kombiniert. Das **Modul 11** zeigt dabei eine Variante der Krankheitslast-Analyse, da hier nicht eine Erkrankung, sondern eine Intervention zur Behandlung der zugrundeliegenden Erkrankung im Fokus der Betrachtung steht. Verschiedene Erkrankungen der Wirbelsäule können operativ behandelt werden. In Folge dieser Operationen können aufgrund von Komplikationen Folgeoperationen notwendig werden. Die vorliegende Studie sollte die jährlich durchgeführten Operationen sowie die Rate gegebenenfalls auftretender Folgeoperationen innerhalb eines Jahres ermitteln. Zusätzlich sollten die Kosten der

Operation erfasst, sowie mit Hilfe eines Kontrollgruppenvergleichs alle in den Routinedaten dokumentierten Folgekosten über einen Zeitraum von zwölf Monaten quantifiziert und die zugrundeliegende Ressourcenverbräuche analysiert werden. Ergänzend wurde untersucht, inwiefern 3D-Bildgebungsverfahren bei den Operationen eingesetzt wurden, um den Vorgang zu unterstützen.

Die durchschnittlichen Kosten der ersten Wirbelsäulenoperation können im Rahmen der Studie mit 11.331 € quantifiziert werden. Im Falle einer notwendigen Folgeoperation (bspw. aufgrund von fehlgesetzten Schrauben zur Fusion der Wirbel) fallen hierfür zusätzliche Kosten in Höhe von 12.291 € im analysierten 1-Jahres-Nachbeobachtungszeitraum an. Die beobachtete Kostendifferenz spiegelt sich in deutlich erhöhten Ressourcenverbräuchen wider. Patienten mit einer Folgeoperation benötigten doppelt so viele Heil- und Hilfsmittel, erhalten mehr Medikamentenverschreibungen und verbringen doppelt so viele Tage im Krankenhaus, wie Patienten ohne Folgeoperation. Die Verwendung von 3D-Bildgebungsverfahren wurde für die einzelnen Verfahren in weniger als 5 % der Operationen dokumentiert. Die Studie zeigt eine deutliche Erhöhung der Krankheitslast für die betroffenen Patienten im Falle einer Folgeoperation. Diese ist zudem mit entsprechenden Kosten für die Kostenträger verbunden. Die oben genannten Zahlen deuten ebenfalls auf die bislang eher seltene Nutzung von 3D-Bildgebungsverfahren im Rahmen der Operationen hin.

Die Studie wurde in der Post-Launch Phase des Market Access Prozess eines Medizintechnikprodukts durchgeführt. Für den Hersteller von 3D-Bildgebungsverfahren ergeben sich aus der Studie vielfältige Anknüpfungspunkte zur Information von betroffenen Patienten, der Ansprache von Krankenhäusern, in welchen die Operationen durchgeführt werden und dem Dialog mit Krankenkassen, welche die Kosten tragen. Bezogen auf die Phase des Market Access Prozesses ist es ebenfalls denkbar, diese Studie in den beiden früheren Phasen des Prozesses durchzuführen, um die Marktpositionierung des Produkts frühzeitig zu unterstützen.

2.4. Einordnung der Module in die Phasen des Market Access Prozess

Die obige Beschreibung der einzelnen Module hat gezeigt, dass die in diese Arbeit einbezogenen Studien überwiegend in der Post-Launch Phase des Market Access Prozess durchgeführt wurden. Ebenfalls deutlich wurde jedoch, dass die Analysen auch zu einem früheren Zeitpunkt genutzt werden könnten, sofern bestimmte Rahmenbedingungen erfüllt sind (z. B. Wettbewerbersituation). So zeigt eine Analyse von

Borchert et al., dass GKV-Routinedaten-basierte Versorgungsforschungsstudien sich in den vergangenen Jahren als Instrument zur Unterstützung des Market Access in der Launch Phase etabliert haben [38]. Abbildung 2 ordnet die Module noch einmal überblicksartig den einzelnen Phasen des Market Access Prozesses zu, in denen sie tatsächlich durchgeführt wurden (Modulnummer mit Studientitel). Ergänzend wird gezeigt, in welchen weiteren Phasen die jeweiligen Studien ebenfalls unterstützende Informationen hätten liefern können (Modulnummer ohne Studientitel).

Tabelle 1: Einordnung der Module in die Phasen des Market Access Prozesses

Phase	Arzneimittel	Impfstoff	Medizintechnik
Pre-Launch	**Modul 1** - Incidence of patients with non-cystic fibrosis bronchiectasis in Germany – A healthcare insurance claims data analysis **Module 2-3** **Modul 4** - Healthcare costs and resource utilization of asthma in Germany: A claims data analysis **Modul 5** - Assessing asthma severity based on claims data: A systematic review	**Modul 8**	**Modul 11**
Launch	**Module 1-5**	**Modul 8**	**Modul 11**
Post-Launch	**Modul 2** - Clinical burden of illness in patients with phenylketonuria (PKU) and associated comorbidities – A retrospective study of German health insurance claims data **Modul 3** - Health economic burden of patients with phenylketonuria (PKU) – A retrospective study of German health insurance claims data **Modul 4** - Healthcare costs and resource utilization of asthma in Germany: A claims data analysis **Modul 5** - Assessing asthma severity based on claims data: A systematic review **Modul 6** - Retrospective analysis into differences in heart failure patients with and without iron deficiency or anaemia	**Modul 7** - Burden of HPV related anogenital diseases in young women in Germany – An analysis of German statutory health insurance claims data from 2012 to 2017 **Modul 8** - Rates of pneumonia among children and adults with chronic medical conditions in Germany **Modul 9** - Vaccination rates and adherence in pneumococcal conjugate vaccination in mature born infants before and after vaccination schedule change – A claims database analysis **Modul 10** - Vaccination rates and adherence in premature infants before and after pneumococcal conjugate vaccine schedule change for term infants – A claims data-base analysis in Germany	**Modul 11** - Burden of disease of reoperations in instrumental spinal surgeries in Germany

Legende: Die tatsächliche Durchführung der jeweiligen Studie ist durch die Modulnummer in Verbindung mit dem Studientitel hervorgehoben. Potenziell weitere mögliche Durchführungszeitpunkte werden durch die Modulnummer ohne Studientitel gekennzeichnet.

3. Beantwortung der Forschungsfrage

Die vorliegende kumulative Dissertation soll das Potential von GKV-Routinedaten-basierten Versorgungsforschungsstudien zur Unterstützung des Market Access von Arzneimitteln, Impfstoffen und Medizintechnikprodukten aus Perspektive der jeweiligen Hersteller untersuchen. In den verschiedenen Phasen des Market Access Prozesses sehen sich die Hersteller von Arzneimitteln, Impfstoffen und Medizintechnikprodukten mit einer Vielzahl von Fragen konfrontiert, die dem Gebiet der Versorgungsforschung zuzuordnen sind. Dies können beispielhaft in zeitlicher Abfolge die folgenden Fragestellungen sein:

- Gibt es einen ungedeckten medizinischen Bedarf in einer bestimmten Indikation?
- Wie werden Patienten in dieser Indikation aktuell behandelt?
- Welche Ressourcen des Gesundheitswesens nehmen diese Patienten in Anspruch?
- Wie hoch sind die spezifischen Krankheitskosten dieser Indikation?
- Wie viele Patienten gibt es aktuell in dieser Indikation (Prävalenz)?
- Wie viele erkranken jährlich neu in dieser Indikation (Inzidenz)?
- Wie effektiv und sicher ist das eigene Arzneimittel unter realen Versorgungsbedingungen?
- Wie unterscheidet sich das eigene Arzneimittel von den Produkten der Wettbewerber unter realen Versorgungsbedingungen?

Wie die einzelnen Module dieser kumulativen Dissertation zeigen konnten, sind GKV-Routinedaten-basierte Versorgungsforschungsstudien zur Beantwortung dieser Fragestellungen geeignet und können im Rahmen des Market Access von Arzneimitteln, Impfstoffen und Medizintechnikprodukten unterstützen. So konnte in Modul 1 bspw. ein ungedeckter medizinischer Bedarf für hospitalisierte NCFB Patienten quantifiziert werden. Ebenso stellt Modul 8 ein Beispiel für die Quantifizierung eines ungedeckten medizinischen Bedarfs bei Risikopatienten dar, welche von einer PCV-Impfung profitieren könnten und die Module 9 und 10 zeigen eine Unterversorgung bei Neugeborenen bezüglich der empfehlungsgerechten Impfung gegen Pneumokokken. Ein Bild der aktuellen Versorgung von Patienten verschiedener Indikationen wird in den Modulen 1, 2 und 6 gezeigt. Die Module 3, 4, 6 und 11 zeigen beispielhaft die Berechnung von Krankheitskosten. Prävalenz- bzw. Inzidenzerhebungen finden sich in den Modulen 1, 2, 3, 6, und 7. Modul 6 ist zudem ein Beispiel einer Effektivitätsbetrachtung unter realen

Versorgungsbedingungen sowie eines Vergleichs verschiedener Behandlungsalternativen. Tabelle 2 zeigt noch einmal überblicksartig die bearbeiteten Fragestellungen für alle Module.

Tabelle 2: Beitrag der einzelnen Module zu potenziellen Fragenstellungen im Rahmen des Market Access

Modul / Kategorie	1	2	3	4	5	6	7	8	9	10	11
Ungedeckter Bedarf	✓	✓			n/a	✓	✓	✓	✓	✓	
Behandlungssituation	✓	✓			n/a	✓			✓	✓	
Ressourcenverbräche	✓		✓	✓	n/a	✓					✓
Krankheitskosten			✓	✓	n/a	✓					✓
Prävalenz		✓	✓		n/a	✓	✓				
Inzidenz	✓				n/a						✓
Sicherheit und Effektivität					n/a	✓					
Comparative Effectiveness					n/a	✓					

Bei der Ausschöpfung des Potentials von GKV-Routinedatenanalysen sind allerdings auch immer die mit den Daten verbundenen Limitationen zu berücksichtigen, wie sie in der Literatur vielfach beschrieben sind. Exemplarisch sollen hier noch einmal das Fehlen von für die Abrechnung irrelevanten Daten wie klinische Parameter, Angaben zur Krankheitsschwere oder ergänzende Charakteristika der Patienten (bspw. Raucherstatus, sozioökonomische Situation, Impfstatus) genannt werden. Ferner Limitationen der Datenstruktur, wie die quartalsweise Dokumentation der Diagnosen im ambulanten Bereich, oder das Fehlen von detaillierten Verordnungsdaten im stationären Bereich. Hinzu kommen Limitationen durch Fehl-, Unter- und Überkodierung von Diagnosen sowie deren Validität. [10, 11, 14, 15, 22, 39-41]

Ergänzend soll an dieser Stelle noch auf mögliche Vorbehalte gegenüber Hersteller finanzierten Studien eingegangen werden, welche die Akzeptanz der Studienergebnisse beeinträchtigen können. Die einzelnen Module wurden alle im Auftrag eines pharmazeutischen bzw. Medizintechnik Herstellers durchgeführt und finanziert. Es handelt sich somit nicht um unabhängige wissenschaftliche Forschung zu den einzelnen Indikationen, sondern um die zielgerichtete Beantwortung relevanter Fragestellungen, welche sich aus Sicht der Hersteller im Rahmen des Market Access Prozesses ihrer Produkte ergeben haben. Zur Sicherung der Qualität von GKV-Routinedaten-basierten Versorgungsforschungsstudien wurden in den vergangenen Jahren jedoch Standards entwickelt, die sowohl die Planung, Durchführung als auch Publikation entsprechender Analysen betreffen. Zu nennen sind hier die Gute Praxis Sekundärdatenanalyse [12], die Gute Epidemiologische Praxis [42] und die in STROSA (STandardized Reporting Of Secondary data Analyses) [43] festgehaltenen Hinweise zum Aufbau und Inhalt von Sekundärdatenanalysen-basierten Publikationen.

Die Entwicklung weitergehender Richtlinien zur Durchführung von Routinedaten-basierten Versorgungsforschungsstudien in den kommenden Jahren ist zu erwarten. Die US-amerikanische Food and Drug Administration (FDA) veröffentlichte unlängst den Entwurf einer Leitlinie zu „*Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products, Guidance for Industry*“ [44] welcher Hinweise zur Wahl und Aufbereitung der Datengrundlage, des Studienzeitraum und der -population, Exposition, Outcomes und Kovariaten gibt. Darüber hinaus wird der Aspekt der Datenqualität behandelt. Dieses Beispiel zeigt die internationalen Bestrebungen, entsprechende Datengrundlagen stärker als bisher auch für den regulatorischen Entscheidungsprozess nutzbar zu machen.

4. Fazit

Im Rahmen dieser kumulativen Dissertation konnte anhand von elf empirischen Beispielen gezeigt werden, dass GKV-Routinedaten-basierten Versorgungsforschungsstudien einen Beitrag zur Unterstützung des Market Access von Arzneimitteln, Impfstoffen und Medizintechnikprodukten leisten können. Die Ausführungen haben ferner gezeigt, dass sich dieses Potential theoretisch in allen Phasen des Market Access Prozesses nutzen lässt, auch wenn die hier vorgestellten Studien vornehmlich in der Post-Launch Phase durchgeführt wurden. Aufgrund der Vorzüge von GKV-Routinedaten-basierten Versorgungsforschungsstudien (kostengünstig, zeitnahe Verfügbarkeit, große Populationen und reale Versorgungssituation) ist davon auszugehen, dass diese auch in der Zukunft zur Unterstützung des Markteintritts von Arzneimitteln, Impfstoffen und Medizintechnik genutzt werden. Hierfür sprechen auch die internationalen Bestrebungen, entsprechende Datengrundlagen stärker als bisher für den regulatorischen Entscheidungsprozess nutzbar zu machen.

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6. Module der kumulativen Dissertation

Modul 1

Diel R, Ewig S, Blaas S, Jacob C, Juelich F, Korfmann G, Sorab S, Sutharsan S, Rademacher J

Incidence of patients with non-cystic fibrosis bronchiectasis in Germany – A healthcare insurance claims data analysis

Respiratory Medicine. 2019; 151: 121-127.

Modul 2

Trefz K, Muntau A, Kohlscheen K, Altevers J, Jacob C, Braun S, Greiner W, Jha A, Jain M,

Alvarez I, Lane P, Schröder C, Rutsch F

Clinical burden of illness in patients with phenylketonuria (PKU) and associated comorbidities – A retrospective study of German health insurance claims data

Orphanet Journal of Rare Diseases. 2019; 14: 181.

Modul 3

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Modul 1

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Incidence of patients with non-cystic fibrosis bronchiectasis in Germany – A healthcare insurance claims data analysis

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ABSTRACT

Background: Incidence and prevalence of patients with non-cystic fibrosis bronchiectasis (NCFB) appear to be increasing worldwide but supporting epidemiological data are scarce. This study assesses the incidence of NCFB patients in Germany in 2013 and analyzes comorbidities and basic patterns of resource use.

Methods: A representative sample of 3.988.648 anonymized persons covered by German public statutory health insurances was used to identify incident patients with NCFB in 2013.

Results: After extrapolation to the general population of the 728 patients found in the reference insurance database, we estimate that a total of 17,095 NCFB patients were newly diagnosed across the country in 2013 as having NCFB. This corresponds to an incidence of 21.23 per 100.000 inhabitants. The majority of NCFB patients (98.4%) was at least 18 years old, and 52.7% of the NCFB patients were male. Trend analysis shows a rise of NCFB incidence in Germany from 2011 through 2013.

COPD (41.4%), asthma (32.8%) and gastroesophageal reflux (18.3%) were the most frequent predisposing conditions. Coronary heart disease was observed in more than one quarter of NCFB patients (28.2%). 58.4% of the NCFB outpatients received antiobstructive inhalative medication. Of the adult NCFB patients, 51.6% were prescribed antibiotics to treat NCFB by settled doctors (outpatient treatment); 51.5% of those patients were males. The peak of antibiotic treatment was observed in the 75–79 age group for males and 70–74 and 75–79 years for females. The majority of diagnosed patients (54.1%) received at least two prescriptions during 2013. Bacterial pathogens were coded for a total of 10.7% of NCFB patients, while *Pseudomonas aeruginosa* was only documented in 2.3%.

Among those diagnosed in 2013, 8.0% of the adult NCFB patients who received antibiotic treatment had to be hospitalized.

Conclusions: Although hospital admissions due to exacerbation in the first year of diagnosing NCFB are not rare, outpatient burden and costs must also be considered a major part of care. Given the increasing recognition of NCFB, a better understanding of the economic burden of the disease is required, with a view towards improving patient management. For this, more detailed, prospective studies are needed.

1. Introduction

Bronchiectasis is a chronic pulmonary disease, defined as permanently dilated airways due to chronic bronchial inflammation. It is primarily the result of a vicious cycle of recurrent infection in the bronchi and bronchioles, inflammation, and bronchial-wall damage. The associated illness is due to retained inflammatory secretions and pathogens that cause obstruction and damage of the airways,

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List of abbreviations

ATC	Anatomical Therapeutic Chemical (ATC) classification system
COPD	Chronic obstructive pulmonary disease
CHD	Chronic heart disease
CF	Cystic fibrosis
CT	Computer tomography
GOLD	Global Initiative for Chronic Obstructive Lung Disease
EBM	Einheitlicher Bewertungsmaβstab [Physicians' Fee Scale within the Statutory Health Insurance Scheme]
DDD	Defined daily dose
DRG	Diagnosis-related group
GBE	Gesundheitsberichterstattung des Bundes [Federal Health Monitoring]
HRCT	High resolution computed tomography
HRI	Health Risk Institute
ICD-10-GM	International Classification of Diseases Version 10 German Modification
NCFB	Non-cystic fibrosis bronchiectasis
OPS	Operationen-und Prozedurenschlüssel [German Operation and Procedure Code]
PZN	Pharmazentralnummer [Pharmaceutical registration number]
SHI	Statutory health insurance

presenting clinically as chronic productive cough, hemoptysis, shortness of breath, and recurrent infectious exacerbations. Bronchiectasis may reflect primary diseases that can affect the lungs. A common and well characterized cause of bronchiectasis is cystic fibrosis (CF). However, bronchiectasis can also be caused by conditions other than CF and is then referred to as non-cystic fibrosis bronchiectasis (NCFB) [1]. CF is excluded as a cause by chloride sweat testing and by genetic testing. In 32–50% of NCFB cases, no underlying conditions can be identified. In these cases, etiology is classified as idiopathic [2,3].

Currently, epidemiological data on incidence and prevalence on NCFB in Europe are scarce. For Germany, only a population-based estimate for the year 2013 is available [4] which shows a prevalence of 67 per 100.000 inhabitants. With respect to incidence in European countries, only Quint et al. [5] reported an increasing incidence (and prevalence) for the UK, focusing on older age groups in the period from 2004 to 2013. Although necessary for assessing required resources for treatment of NCFB within the various European healthcare systems in the future, real-life data on the upcoming burden of NCFB in Europe are completely lacking. Therefore, this study aims to assess overall incidence of NCFB in Germany.

Secondary objectives are to characterize the patient population regarding clinical and demographic variables, i.e. age, sex, comorbidities, past claims of high resolution computed tomography (CT/HRCT), use of antiobstructive inhalants, and antimicrobial treatment. Furthermore, subpopulations of NCFB patients were identified according to the degree of severity (e.g. prescriptions of antibiotic therapies, hospitalizations due to NCFB under antibiotic treatment) by using a six-level patient flowchart design. In addition, we analyzed the development of NCFB incidence over time between 2011 and 2013.

2. Methods

2.1. Setting and data collection

This retrospective cohort study is based on the Health Risk Institute (HRI) research database from more than 80 German statutory health insurances companies (SHI) and thus represents approximately 4.9% of the German population. Statutory health insurances cover 87% of the German population, i.e., 69.9 million individuals) and provide nearly full coverage for all health care services. Patient data in Germany are pooled and transferred to the SHI on a quarterly basis. The sample we obtained of the HRI health claims database provides anonymized billing data from longitudinally linked records of 3.988.648 members and is representative for the German population in terms of age and gender using the age and gender distribution as per December 31, 2011, as provided by the Federal Statistical Office [6]. Privately insured patients are not included in this database.

Out of our database patients with bronchiectasis were included in

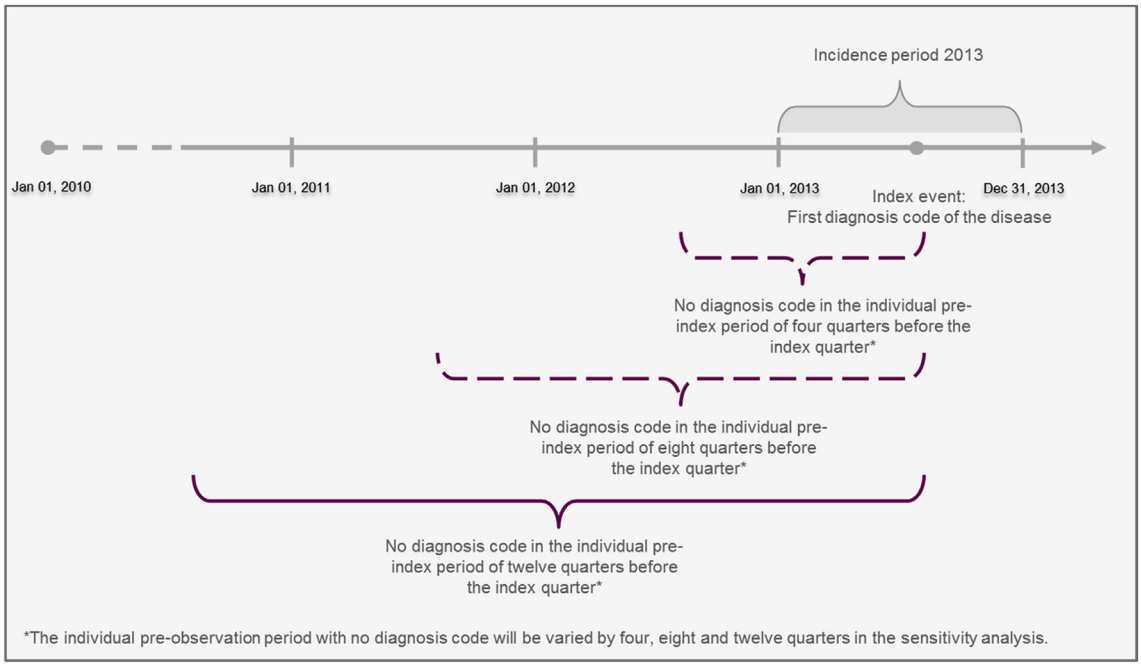

Fig. 1. Sensitivity analysis for the pre-index period.

our study analysis if they had at least one medical claim with a documented ICD-10 GM code J47 Bronchiectasis or Q33.4 (congenital bronchiectasis) as an inpatient (primary or secondary diagnosis) or at least two as an outpatient in an index quarter in 2013 and if there was no prior diagnosis of J47 or Q33.4 for such a patient within 3 years preceding the date of diagnosis in 2013.

Specific information related to the setting of care is available for inpatient care, including records that summarize hospital admission information such as the International Statistical Classification Of Diseases And Related Health Problems, 10th revision, German Modification (ICD-10-GM) code in primary or secondary position, and Diagnosis Related Group (DRG) code. Information on outpatient services contains procedures performed (e.g. laboratory services, radiology, echocardiography) by uniform assessment standard codes ("Einheitlicher Bewertungsmaβstab") and day of performance. Pharmacotherapy of outpatients is documented on a package level for each drug dispensed by "Pharmazentralnummer (PZN)" codes which can be linked to the German Anatomical Therapeutic Chemical (ATC)-Classification codes and defined daily doses (DDDs). Furthermore, the day of prescription, day of dispensing, and costs of drugs dispensed from a statutory health insurance perspective, without individual deductibles between single sickness funds and pharmaceutical companies, are recorded.

2.2. Assessment of patients with first diagnosis of NCFB

Patients with bronchiectasis were classified as having bronchiectasis if they met the following criteria: (a) at least one medical claim with a documented ICD-10 GM code J47 bronchiectasis or Q33.4 congenital bronchiectasis as an inpatient (primary or secondary diagnosis) or at least one assured diagnosis as an outpatient in an index quarter in 2013. We sought to avoid including patients who had been diagnosed prior to 2013 as having bronchiectasis but were not immediately treated, becoming subsequently falsely classified in 2013 after a latency period as "new" cases. Hence we performed a sensitivity analysis for choosing the best possible pre-index period: When varying between four and twelve pre-index quarters with no previous diagnosis for bronchiectasis before the first (index) quarter in 2013 (see Fig. 1) a three year pre-index period was chosen as cutoff in which the highest number patient was classified incorrectly as "incident" compared to a pre-observation period of only one deductible year (3.9% compared to 2.6%).

2.3. Patient flowchart analysis

A six-level patient flowchart design was used to stratify incident patients with bronchiectasis, with the aim of identifying NCFB incidence and patient subgroups, e.g. with antibiotic treatment. Fig. 2 includes the identification and analyses of incident patients, which are described in the following sections.

In the first step, all incident patients with bronchiectasis in 2013 were identified by ICD-10-GM codes J47 bronchiectasis or Q33.4 congenital bronchiectasis during the period of January 1 until December 31, 2013 (F1). According to the results of the sensitivity analysis, patients were also excluded if the ICD-10-GM diagnosis code was present in an individual pre-observation period of twelve quarters prior to the index event. These patients were further analyzed to identify patients with NCFB (F2) according to age and sex. Individuals were excluded if an ICD-10-GM diagnosis code E84 Cystic fibrosis was assigned in the inpatient sector (primary or secondary diagnosis) or outpatient sector (verified diagnosis). Additional analyses were performed to describe the age and gender distribution of NCFB patients, the use of antiobstructive inhalants and antibiotics, existing comorbidities, coding of bacterial agents as the cause of infections in NCFB patients, and the utilization of computed tomography or HRCT scans to verify NCFB diagnosis for incident patients. To assess the treatment of NCFB patients with inhalative medications, agents were selected based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report [7] and were identified on the basis of ATC codes. Referring to Ringhausen et al. [4], the most common pulmonary or cardial conditions associated with or predisposing to NCFB were determined in those patients.

To evaluate the utilization of CT and/or HRCT for the verification of NCFB diagnosis, the proportion of incident patients with an EBM code 34330 CT examination of the thorax in an individual timeframe of one quarter before the index quarter and the index quarter itself was identified. The (voluntary) notification of bacterial agents (B96.-!) by physicians in private practice for documenting infection in NCFB patients was counted during an individual timeframe of one quarter before the index quarter, the index quarter itself and the quarter subsequent to the index quarter. Finally, the prescription of antiobstructive inhalants was analyzed for the period of the individual index quarter as well as all following quarters until the end of the observation period (December 31, 2013).

With the next step (F3), all patients under the age of 18 years were excluded to focus on the adult NCFB population.

In the next step (F4), antibiotic treatment of adult NCFB patients was assessed. Patients were classified according to age and sex as well as the number of antibiotic prescriptions from the index quarter until

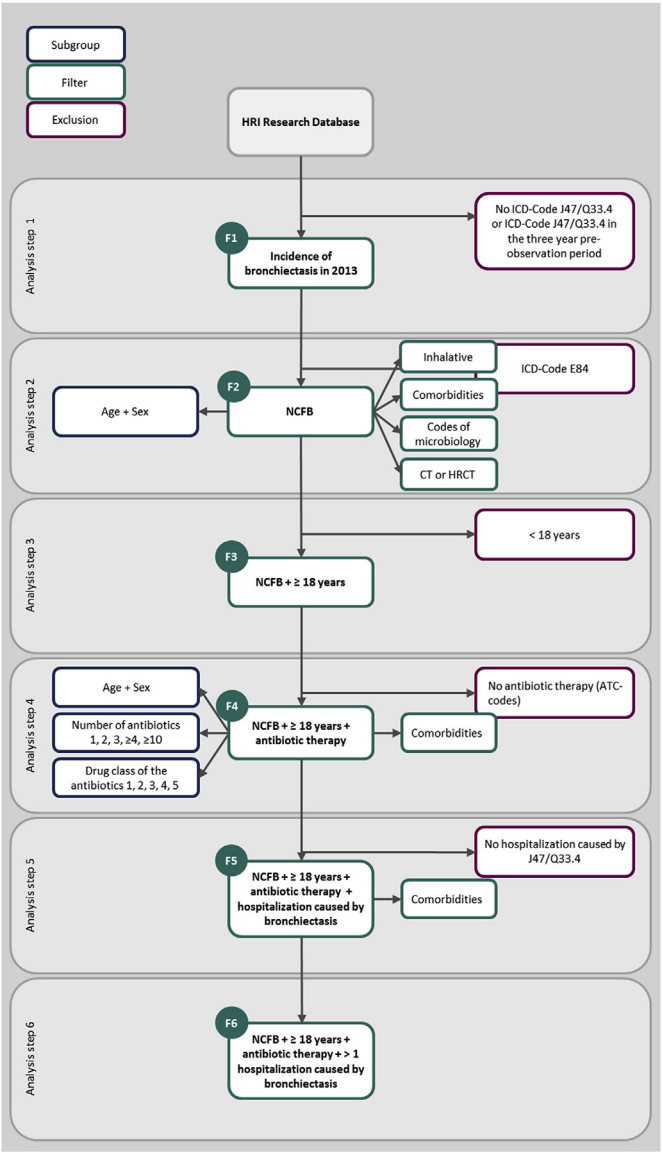

Fig. 2. Flow chart analysis for the year 2013.

December 31, 2013.

Antibiotics were identified by ATC codes (see Appendix Table 1) based on the German guidelines for the treatment of community acquired lower respiratory tract infections and pneumonia ([10]. These include cephalosporins as optional treatment [10], as well as antibiotic prescriptions categorized into five antibiotic drug classes which include amino-penicillin or aminopenicillin with beta-lactamase inhibitor, doxycycline, macrolide, fluoroquinolone, and cephalosporin (see Appendix Table 2). To concentrate on individuals with antibiotic treatment due to NCFB, patients were only included if they had at least one prescription claim without a concurrent ICD-10-GM diagnosis code for urinary tract infections (N10 Acute tubulo-interstitial nephritis, N30.0 Acute Cystitis, N39.0 Urinary tract Infection, site not specified and N41.- Inflammatory diseases of prostate in the same quarter were excluded in this sub-analysis) to exclude the possibility of antibiotic treatment for common causes other than lower respiratory tract infections and pneumonia.

Additional analysis was performed to assess comorbidities in those NCFB patients aged 18 years or older with antibiotic treatment in the four quarters before the individual index quarter based on ICD-10-GM coding.

To identify in the next step (F5) a subpopulation of NCFB patients with exacerbations, hospitalization of patients that occurred despite ongoing antibiotic treatment based on a primary diagnosis of J47 bronchiectasis or Q33.4 congenital bronchiectasis were assessed during the timeframe of January 1, 2013 until December 31, 2013. In addition, in the last step (F6), the number of patients under antibiotic treatment - and due to an even more severe degree of the disease - with more than one hospitalization caused by J47 or Q33.4 in that timeframe, was analysed.

2.4. Extrapolation to the German population

The results of the database analysis were extrapolated to the German population using the formula:

$$\frac{\text{Patient count} * \text{German population}}{\text{HRI research data sample}}.$$

Confidence intervals with 95% confidence level were calculated by applying the Clopper-Pearson-Interval. Data on the German population was derived from the Federal Statistical Office [8,9].

2.5. Trend analysis

A trend analysis for incidence was performed over the course of the two preceding years, 2011 and 2012, comparing the incident patient numbers of the HRI database for the respective year with that of 2013.

3. Results

3.1. Incidence assessment and trend analysis

In 2013, an estimated population (by extrapolation) of 17.353 individuals was newly diagnosed with bronchiectasis in Germany, resulting in an incidence of 21.55 patients per 100.000 inhabitants. The majority of patients (98.9%) was diagnosed with ICD-10-GM code J47 bronchiectasis, whereas Q33.4 (congenital bronchiectasis) was a rather uncommon condition (0.23%). After exclusion of CF-patients, the estimate of patients classified as having NCFB reached 17,095, which corresponds to an incidence of 21.23 per 100.000 persons (see Table 1). 52.7% of the reference NCFB patients (384/728 NCFB patients of the examined HRI database) were male. The majority of NCFB patients (716/728, or 98.4%) was above the age of 18 years. The different ages of the cases are seen in Table 2. The incidence per 100.000 adults was calculated to be 20.88 patients. The trend analysis of the SHI data showed a rise of NCFB incidence in Germany 2012 to 2013, whilst the incidence from 2011 to 2012 had remained stable (Table 3).

Table 2
Demographic characteristics of incident NCFB patients.

Age group	Male	Female	Total
< 20 years	6	7	13
20–24 years	1	5	6
25–29 years	2	4	6
30–34 years	9	7	16
35–39 years	2	5	7
40–44 years	6	7	13
45–49 years	17	17	34
50–54 years	27	20	47
55–59 years	30	28	58
60–64 years	43	37	80
65–69 years	51	48	99
70–74 years	73	53	126
75–79 years	68	57	125
80–84 years	32	26	58
85–89 years	16	15	31
≥90 years	1	8	9
Total	384	344	728

3.2. Comorbidities and inhalative medication

A HRCT to assist in confirming the diagnosis of NCFB was recorded in 41.5% (302/728) of the cases. COPD (J.44.-; 301/728, or 41.3%) and asthma (J.45.-; 239/728, or 32.8%) were the most frequent predisposing comorbidity conditions followed by gastroesophageal reflux (K21.- which was coded in 18.3% of cases (Table 4). Coronary heart disease (CHD) was observed in 204/728, or 28.2%, i.e. in more than one quarter of NCFB patients. According to the high number of underlying obstructive diseases, 58.4% of the NCFB patients received antiobstructive inhalative medication (Table 5).

3.3. Bacterial infections

Bacterial agents as the cause of diseases were recorded in only 10.7% of the cases. Of those 11 patients (1.48%) had *Haemophilus* and 18 (2.4%) had *Pseudomonas aeruginosa* (Table A3).

Table 1
Incidence of bronchiectasis in Germany 2013.

Label	Incidence 2013	95% confidence interval		Incidence (per 100,000)[a]
Bronchiectasis	17,353	16,125	18,651	21.55
NCFB	17,095	15,876	18,439	21.23
NCFB ≥ 18 years	16,813	15,604	18,146	20.88
NCFB ≥ 18 years with antibiotic therapy	8759	7892	9724	10.88
NCFB ≥ 18 years with antibiotic therapy and hospitalization caused by bronchiectasis	704	475	1009	0.87
NCFB ≥ 18 years with antibiotic therapy and more than one hospitalization caused by bronchiectasis	70	15	206	0.09

[a] This number refers to the entire population (enrollees observable for three years prior to 01.01.2013).

Table 3
Trend analysis of the incidence of NCFB in Germany for 2011–2013.

Year	Incident patients in the HRI research database	$n_{extrapolated}$ for the German population	95% confidence interval		Incidence (per 100,000)
2011	540	13,710	12,578	14,917	16.77
2012	548	12,896	11,839	14,022	16.05
2013	728	17,353	16,125	18,651	21.23

3.4. Antibiotic treatment

51.6% of the adult NCFB patients received antibiotic treatment through prescription by settled doctors; 51.5% of those patients were males. The peak of antibiotic treatment was observed in the age group of 75–79 years for males and 70–74 as well as 75–79 years for females. Forty-six percent (45.9%) of the patients received only one prescription of antibiotics whereas the majority (54.1%) received at least two separate prescriptions in 2013 (Table 6).

With exception of doxycycline, which was prescribed only in 9.24% of the patients, antibiotics of all other groups were frequently prescribed. Their frequencies ranged from 43.5% of NCFB cases (for macrolides) to nearly two thirds (for fluoroquinolones) (65.8%, see Table 7).

3.5. Hospital resource use

NCFB-related hospitalizations in incident patients, i.e. by definition firstly diagnosed in 2013, were estimated 4.1% of all NCFB cases (704/17,095) and 8.0% of adult NCFB patients under antibiotic treatment (704/8759), the latter showing a possibly higher disease severity. These patients frequently suffered from asthma (50%) and COPD (43.3%). Incidence of those patients was 0.87 per 100,000 inhabitants. As expected, newly diagnosed NCFB patients with more than one NCFB-related hospitalization in 2013 were rare with 0.4% (70/17,095) corresponding to an incidence of 0.09 patients per 100,000 inhabitants.

4. Discussion

To date, epidemiological data on the incidence of NCFB are scarce worldwide. With the exception of Quint's recently published UK paper [5] and Weycker's estimation of 2013 NCFB incidence in US adults [11] such data in other countries are either outdated [12] or present only subgroups: Twiss et al. reported an incidence of bronchiectasis for children under the age of 15 years of 3.7 per 100,000 per year in New Zealand [13]. Thus, the objective of this study was to estimate the current incidence of NCFB in Germany from a representative sample of insured German residents, together with comorbidities and some key features of resource use due to NCFB.

Whereas NCFB has previously been neglected and classified as an “orphan disease”, our study results support the assumption that it is much more frequent. Not only appears the prevalence in Germany [4] and in the UK [5] to be increasing, but – according to our results – also the incidence, with 21.23 newly diagnosed patients per 100,000 persons in Germany in 2013. As HRCT was used to assist in confirming the diagnosis of NCFB in 41.5% of the incident cases, the increasing incidence may in part be explained by the more accurate diagnostic approach and therefore requires confirmation over a longer period.

Table 5
Inhalative medications of incident NCFB patients.

ATC Code	Description	N	%
R03AC	Selective beta-2-adrenoreceptor agonists	425	58.38
R03AK	Sympathomimetics and other drugs for obstructive airway diseases		
R03BA	Glucocorticoids		
R03BB	Anticholinergics		
No inhalative medications		303	41.62

Table 6
Frequency of antibiotic prescriptions.

Number of prescriptions	N	%
One prescription	169	45.92
Two prescriptions	100	27.17
Three prescriptions	53	14.40
At least four prescriptions	46	12.50
At least ten prescriptions	2	0.54
Total	368	100.00

Table 7
Antibiotic prescribed separated by drug classes.

Drug Class	N	%
1 - Aminopenicillin/Aminopenicillin with beta-lactamase inhibitor	187	50.82
2 - Doxycycline	34	9.24
3 – Macrolide	160	43.48
4 – Fluoroquinolone	242	65.76
5 – Cephalosporin	164	44.57
Total	368	100.00

Table 4
Comorbidities of incident NCFB patients[a].

ICD-10-GM Code	Description	N	%
J41.- or J42	Simple and mucopurulent chronic bronchitis or Unspecified chronic bronchitis	106	14.56
J43.-	Emphysema	82	11.26
J44.-	Other chronic obstructive pulmonary disease	301	41.35
J45.-	Asthma	239	32.83
K21.-	Gastro-oesophageal reflux disease	133	18.27
M06.-	Other chronic polyarthritis	40	5.49
D80.-	Immunodeficiency with predominantly antibody defects	7	0.96
R04.2	Haemoptysis	21	2.88
I50.-	Heart failure	115	15.80
I20.- to I25.-	Angina pectoris, Acute myocardial infarction, Subsequent myocardial infarction, Certain current complications following acute myocardial infarction, Other acute ischaemic heart diseases, Chronic ischaemic heart disease	204	28.02
Total (Individuals with comorbidities)		548	75.27

[a] Multiple entries are possible.

However, the prevalence of COPD was notified in a high proportion (44.1%) of the newly diagnosed NCFB patients as underlying disease and is still increasing worldwide [14]; thus, the number of NCFB patients can also be expected to climb in the next future. Without any doubt, a rising number of patients also requires a better understanding of the distribution and the quantities of NCFB-induced healthcare resources.

Hospitalizations are considered as main cost drivers, especially in patients who are subject to frequent exacerbations [15,16]. It is of note, that even during the first year (2013) of establishing the NCFB-diagnosis, 8.0% (704/8759) of the adult NCFB patients who were under antibiotic treatment experienced exacerbations and had to be hospitalized. However, the high proportion of outpatients who were administered antibiotics belonging to 4 out of 5 relevant drug classes indicates that hospitalization for treating exacerbations only represents a limited part of NCFB management of NCFB patients. The high number of antibiotic prescriptions – 45.9% of patients had received at least one prescription of antibiotics in 2013, but more than one half (54.1%) had received at least two prescriptions – demonstrates that the economic burden of NCFB is not well captured when the focus is placed primarily on hospitalization.

Patients with bronchiectasis are frequently chronically infected with bacterial pathogens [17]. In Europe, *P. aeruginosa* affects up to 20% of patients with bronchiectasis [18]. Thus, the prevalence of associated bacterial infections in our database of 10% overall and only 2.4% coded infections with *P. aeruginosa* was lower than expected. This difference can partly be explained by a probable underestimation, as bacterial coding by physicians is voluntary. It may, however, be speculated that only a fraction of patients with bronchiectasis is susceptible to the persistent *P. aeruginosa* infection that is more frequent in patients with more extensive bronchiectasis [19]. Due to the low number of bacterial coding, a firm conclusion on chronic bacterial infection cannot be given. On the other hand there is a high quinolone use in relation to the frequency of bacterial cultures. Microbiological examination should be done in all patients with bronchiectasis at least once a year.

The results of our representative analysis confirm the impact of underlying comorbidities, such as COPD, asthma and gastroesophageal reflux which may play an important role in the progression of bronchiectasis [20]. In addition, more than one quarter of NCFB patients suffered from coronary heart disease (CHD). This is more important, as a recently published UK study [21] found that the rate of first time cardiovascular events (myocardial infarction or stroke) following a respiratory tract infection in NCFB patients is 56% higher than that of the general population.

Our study has several limitations. First, we had a very short time period from 2011 to 2013 to make a conclusion about the rising incidence of bronchiectasis in Germany. This is why we call it as a trend of higher incidence. Second, the number of HRCT done is low although it is the gold standard in diagnosing bronchiectasis. Bronchiectasis is still an underdiagnosed disease. It is not to be assumed that the incidence of this analysis is too high due to a low CT rate. Third, it was also not possible to determine the hospitalization and antibiotic use of a single comorbidity separately. Finally, depending on ICD-10 diagnosis codes, our study is most likely still underestimating the true incidence of bronchiectasis in Germany. ICD codes are primarily used for reimbursement purposes.

In conclusion, the incidence of NCFB in Germany appears to be rising. NCFB patients have a considerable resource use by antibiotic treatment in the outpatient setting, even during the first year of establishing the diagnosis. The number of hospitalizations due to exacerbations treated with antibiotics is still low with 8% in that first year, but its development in the future depends on the extent to which NCFP patients receive optimal care. Matched observational studies with a nested case-control design including the impact of indirect sick leave costs are required to take into account the full spectrum of interventions and their associated costs.

Conflicts of interest

RD and JR received fees for lectures and/or consultancy from Bayer Vital and INSMED.

SB, SE, SSo and SSu received fees for lectures and/or consultancy from Bayer Vital.

FJ and GK are employees of BAYER Vital GmbH. CJ is an employee of Xcenda GmbH paid by Bayer Vital GmbH for collecting and analyzing statutory health insurance data.

Authors' contribution

CJ, FJ, and GK developed the study protocol. RD and JR analyzed and interpreted the patient data and wrote the manuscript. SE, CJ, FJ, GK, SB, SSu, SSo analyzed and interpreted the patient data, revised the manuscript and gave final approval.

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Appendix A. Supplementary data

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Modul 2

Clinical burden of illness in patients with phenylketonuria (PKU) and associated comorbidities – A retrospective study of German health insurance claims data

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Clinical burden of illness in patients with phenylketonuria (PKU) and associated comorbidities - a retrospective study of German health insurance claims data

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Abstract

Background: Phenylketonuria (PKU) is an inherited deficiency in the enzyme phenylalanine hydroxylase (PAH), which, when poorly-managed, is associated with clinical features including deficient growth, microcephaly, seizures, and intellectual impairment. The management of PKU should start as soon as possible after diagnosis to prevent irreversible damage and be maintained throughout life. The aim of this study was to assess the burden of illness in PKU patients in general and in PKU patients born before and after the introduction of newborn screening in Germany.

Methods: This retrospective matched cohort analysis used the Institut für angewandte Gesundheitsforschung Berlin (InGef) research database containing anonymized healthcare claims of approximately 4 million covered lives. PKU patients were compared with matched controls from the general population within the same database (1:10 ratio via direct, exact matching on age and gender without replacement). PKU patients were included if they were aged ≥18 years on 01/01/15 and were continuously enrolled from 01/01/10 to 31/12/15. The 50 most commonly reported comorbidities and 50 most commonly prescribed medications in the PKU population were analyzed. Differences between groups were tested using 95% confidence interval (CI) of prevalence ratio (PR) values.

Results: The analysis included 377 adult PKU patients (< 5 of which were receiving sapropterin dihydrochloride) and 3,770 matched controls. Of the 50 most common comorbidities in the PKU population, those with a statistically significant PR > 1.5 vs controls included major depressive disorders (PR = 2.3), chronic ischemic heart disease (PR = 1.7), asthma (PR = 1.7), dizziness and giddiness (PR = 1.8), unspecified diabetes mellitus (PR = 1.7), infectious gastroenteritis and colitis (PR = 1.7), and reaction to severe stress and adjustment disorders (PR = 1.6). The most commonly prescribed Anatomical Therapeutic Chemical (ATC) subcodes among PKU patients (vs the control population) are for systemic antibacterials (34.7% vs 32.8%), anti-inflammatory and antirheumatic (29.4% vs 27.5%), renin-angiotensin agents (30.0% vs 27.0%), acid-related disorders (29.4% vs 20.2%), and beta-blockers (24.9% vs 19.9%).

Conclusion: The overall clinical burden on patients with PKU is exacerbated by a significantly higher risk of numerous comorbidities and hence, prescribing of the requisite medication, both for recognized (e.g. major depressive disorders) and more unexpected comorbidities (e.g. ischemic heart disease).

Keywords: Phenylketonuria, Burden of illness, Burden of disease, Claims data, Statutory health insurance, Hyperphenylalaninemia

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Background

Phenylketonuria (PKU) is, in 98–99% of cases, due to an inherited deficiency in the enzyme phenylalanine hydroxylase (PAH), which results in elevated levels of the essential amino acid phenylalanine (Phe) and reduced levels of tyrosine [1]. PKU is caused by over 1,000 different gene variants of PAH [2] and the severity of the resulting disease ranges from mild to severe, based on the residual enzyme activity and the level of Phe circulating in the blood (blood Phe) [1, 3]. High blood Phe levels alter large neutral amino acid (e.g. tyrosine, tryptophan) transfer across the blood-brain barrier and interfere with the production of neurotransmitters. To this end, high blood and brain Phe concentrations in patients with PKU are associated with deleterious effects on neurocognitive outcomes [3].

Management of PKU should be maintained throughout life and should start as soon as possible after diagnosis via newborn screening (NBS) to prevent irreversible damage, such as neurological impairment and mental retardation [4, 5]. Besides the start of an early treatment, strict blood Phe control is of primary importance for an optimal outcome, particularly during the first years of life [5]. The management of PKU comprises the reduction of dietary intake of Phe by low-protein diets and Phe-free amino acid supplements, and may include low-protein supplements/foods. Additionally, sapropterin dihydrochloride (sapropterin, Kuvan®, BioMarin Pharmaceutical Inc., Novato, CA, USA), a synthetic version of BH4, the naturally occurring co-factor of PAH, can be used in responsive patients to stimulate residual PAH activity [6, 7]. Dietary management options are ineffective in many adults with PKU due to long-term adherence issues [8–10] or inadequate Phe-lowering effects [6]. Moreover, a longtime Phe-restricted diet is associated with vitamin and/or mineral deficiencies [11, 12].

The impact of the disease on individual patients and the healthcare system as a whole can only be understood when considering all associated comorbidities that affect patients. PKU is often associated with neuropsychiatric, behavioral and cognitive symptoms, but the full range of systemic comorbidities associated with PKU and long-term exposure to elevated blood Phe are poorly understood.

The aim of this study was to assess the comorbidity profile of adult PKU patients in Germany and gain insights into the burden of illness in PKU patients.

Results

Patient populations and general health

Overall, 3,723,345 individuals in the InGef research database were continuously enrolled during the study period from January 1st, 2015 until December 31st, 2015. Thereof, 377 adult individuals with PKU were identified, resulting in a period prevalence of 10.13 in 2015 (per 100,000 individuals). Most adult PKU patients were female (58.1%) and the mean age of adult PKU patients in 2015 was 50.9 ± 20.4 years (Table 1).

From the 377 patients in the adult PKU cohort, 161 (42.7%) patients were born in 1969 (implementation of NBS) or later (presumed to be early-diagnosed) and 216 (57.3%) patients were born prior to 1969 (presumed to be late-diagnosed). Due to this classification by birth year, the mean age of early-diagnosed patients (30.7 ± 8.2 years) was less than half that of the late-diagnosed patients (65.9 ± 12.1 years; Table 1). Additionally, there was a higher proportion of females in the early-diagnosed group ($n = 101$; 62.7%) than in the late-diagnosed group ($n = 118$; 54.6%). Less than 1.3% of the overall population were receiving sapropterin (< 5 patients; specific number not identified in this study due to patient privacy). All patients receiving sapropterin were early-diagnosed patients. While 52 (13.8%) patients in the overall PKU population were receiving D.A.S. (Phe-free Dietary Amino Acid Supplement), these were mainly in the early-diagnosed group ($n = 47$, 29.2% of early-diagnosed patients vs $n = 5$, 2.3% of the late-diagnosed patients).

When assessing the Updated Charlson Comorbidity Index (CCI) for the adult PKU cohort, the PKU cohort shows a higher burden of the CCI constituent comorbidities compared to the matched cohort (Table 2). The PKU cohort shows significantly more comorbid burden than controls (20.2% vs 13.1% with CCI scores ≥3). The late-diagnosed PKU patients have a significantly higher comorbid burden compared with their matched controls, especially in terms of severity (33.8% vs 22.3% of subjects had a CCI score ≥ 3; CCI categories among the late-diagnosed PKU cohort and the matched cohort are shown in Additional file 1: Table S1).

There were no significant differences in comorbid burden between early-diagnosed PKU patients and their matched controls (Additional file 1: Table S2). Unsurprisingly, given the markedly younger age of the early-diagnosed cohort (mean age 30.7 years), they had a lower comorbid burden than the late-diagnosed cohort (mean age 65.9 years)

Table 1 Age and gender of PKU patients in total PKU population, early-diagnosed, and late-diagnosed patients

		PKU patients ($n = 377$)	Early-diagnosed PKU patients ($n = 161$)	Late-diagnosed PKU patients ($n = 216$)
Gender	Female, n (%)	219 (58.1)	101 (62.7)	118 (54.6)
	Male, n (%)	158 (41.9)	60 (37.2)	98 (45.4)
Age (years)	Mean (SD)	50.9 (20.4)	30.7 (8.2)	65.9 (12.1)
	Median	51	30	65
	Range	18–96	18–46	46–96

Table 2 Updated CCI categories among the PKU cohort and the matched cohort

	PKU patients (*n* = 377)		Control group (*n* = 3,770)		Chi^2 test *p value*	PR (95% CI)
	n	%	*n*	%		
CCI = 0	194	51.5	2,206	58.5	0.001	0.9 (0.79–0.97)
CCI = 1	72	19.1	716	19.0	1.000	1.0 (0.81–1.25)
CCI = 2	35	9.3	353	9.4	1.000	1.0 (0.71–1.38)
CCI = 3	30	8.0	189	5.0	0.021	1.6 (1.10–2.30)
CCI ≥ 4	46	12.2	306	8.1	0.009	1.5 (1.12–2.01)

CCI of 0 = no comorbidities, ≥4 = severe comorbidities

and no patients had a CCI score ≥ 3 (vs 33.8% in the late-diagnosed cohort).

Comorbidity profile

Adult PKU patients

The analysis included 377 adult patients with PKU and 3,770 matched control subjects. The most common comorbidities were assessed by identifying the 50 most prevalent comorbidities among adult PKU patients in 2015 in the database. More than a third (38.7%) of adult PKU patients suffered from essential (primary) hypertension, dorsalgia (35.3%), and disorders of lipoprotein metabolism and other lipidemias (33.7%). The full list of the 50 most prevalent comorbidities is shown in Additional file 1: Table S3 and those that were present in > 10% of the adult PKU patients are shown in Table 3.

Among the comorbidities that were present in > 10% of the PKU cohort, those that were significantly more prevalent in the PKU vs control population included: chronic ischemic heart disease (Prevalence = 15.7%; PR = 1.7; 95% CI 1.35–2.25); asthma (Prevalence = 11.9%; PR = 1.7; 95% CI 1.26–2.29); dizziness and giddiness (Prevalence = 11.1%; PR = 1.8; 95% CI 1.35–2.52); unspecified diabetes mellitus (Prevalence = 10.9%; PR = 1.7; 95% CI 1.23–2.31); reaction to severe stress and adjustment disorders (Prevalence = 10.9%; PR = 1.6; 95% CI 1.15–2.14); infectious gastroenteritis and colitis (Prevalence = 10.6%; PR = 1.7; 95% CI 1.23–2.33); and adverse effects, not elsewhere classified (Prevalence = 10.1%; PR = 1.7; 95% CI 1.23–2.37) (Fig. 1). Additionally, comorbidities in the top 50 most common in the PKU population with a PR > 1.5 for the PKU cohort compared with the matched controls, but not shown in Table 3 (i.e. present in < 10% of PKU patients), included other acquired deformities of limbs (Prevalence = 9.8%; PR = 2.2; 95% CI 1.60–3.15), other chronic obstructive pulmonary disease (Prevalence = 9.5%; PR = 1.9; 95% CI 1.34–2.65), other anxiety disorders (Prevalence = 9.3%; PR = 1.8; 95% CI 1.29–2.56), and major depressive disorders, recurrent (Prevalence = 8.8%; PR = 2.3; 95% CI 1.57–3.25).

The 50 most frequently prescribed agents in PKU patients are provided in full in Additional file 1: Table S4 and those prescribed in > 10% of PKU patients in Table 4. The most common Anatomical Therapeutic Chemical (ATC) categories of prescribed agents that are significantly more prevalent in PKU vs controls are cardiovascular (43.8% vs 37.4%; PR 1.17; 1.04, 1.32), nervous system (40.3% vs 28.4%; PR 1.42; 95% CI 1.24, 1.62), alimentary tract and metabolism (40.6% vs 29.6%; PR 1.37; 95% CI 1.20, 1.56), and dermatologicals (22.0% vs 15.5%; PR 1.41; 95% CI 1.15, 1.73). The most common ATC subcodes for the prescribed agents with significant differences between the PKU and control populations are for acid-related disorders (29.4% vs 20.2%; PR 1.46; 95% CI 1.23, 1.72) and analgesics (24.4% vs 19.0%; PR 1.28; 95% CI 1.06, 1.55). Additionally, beta-blockers, lipid-modifying agents, diuretics, calcium channel blockers, cardiac therapy, vitamins, minerals, pyschoanaleptics, psycholeptics, antiepileptics, other nervous system drugs, vaccines, antigout preparations, corticosteroids for systemic use, corticosteroid dermatological preparations, antimycotics for dermatological use, and gynecological antiinfectives and antiseptics were all prescribed significantly more often in the PKU vs control populations.

Early-diagnosed adult PKU patients

Twenty-one of the top 50 comorbidities in the early-diagnosed PKU patients were present in > 10% of the population and are shown in Table 5. The most common recorded ICD-10-GM codes among the early-diagnosed PKU patients were encounters for contraceptive management (Prevalence = 46.6%) and screening for malignant neoplasms (Prevalence = 35.4%). Furthermore, other non-inflammatory disorders of vagina is among the top 3 most frequently recorded ICD-10-GM codes. There was a higher proportion of female patients among early-diagnosed adult PKU patients and there were more female-specific conditions in this population, such as for contraception. However, none of these conditions were significantly different between early-diagnosed PKU patients and their matched control group.

Among the 21 most frequently coded ICD-10-GM-codes that occurred in > 10% of the early-diagnosed PKU population, those with a significant PR were: encounter for other

Table 3 Comorbidity profile[a] of adult PKU patients and matched controls in Germany in 2015

ICD-10-GM code	Comorbidity	PKU population ($n = 377$)	Control population ($n = 3,770$)	PR (95% CI)
		%	%	
I10	Essential (primary) hypertension	38.7	36.2	1.07 (0.94, 1.22)
M54	Dorsalgia	35.3	30.3	1.16 (1.01, 1.34) [b]
E78	Disorders of lipoprotein metabolism and other lipidemias	33.7	25.1	1.34 (1.15, 1.56) [b]
Z12	Encounter for screening for malignant neoplasms	31.3	30.0	1.04 (0.89, 1.22)
H52	Disorders of refraction and accommodation	27.3	23.6	1.16 (0.97, 1.38)
Z30	Encounter for contraceptive management	22.5	21.2	1.06 (0.87, 1.30)
N89	Other noninflammatory disorders of vagina	21.8	18.0	1.21 (0.99, 1.48)
J06	Acute upper respiratory infections of multiple and unspecified sites	21.5	18.8	1.14 (0.93, 1.40)
Z01	Encounter for other specified exam without complaint, suspected or reported dx	20.7	14.0	1.47 (1.19, 1.82) [b]
F32	Major depressive disorder, single episode	16.2	13.3	1.22 (0.95, 1.55)
Z00	Encounter for general exam without complaint, suspected or reported dx	15.9	14.4	1.11 (0.87, 1.42)
E66	Overweight and obesity	15.9	11.2	1.43 (1.11, 1.83) [b]
I25	Chronic ischemic heart disease	15.7	9.0	1.74 (1.35, 2.25) [b]
F45	Somatoform disorders	15.4	12.1	1.27 (0.98, 1.63)
E11	Type 2 diabetes mellitus	14.9	11.6	1.28 (0.99, 1.66)
Z25	Need for immunization against other single viral diseases	14.3	13.1	1.09 (0.84, 1.42)
M53	Other and unspecified dorsopathies, not elsewhere classified	14.3	10.2	1.40 (1.08, 1.83) [b]
E04	Other nontoxic goiter	14.1	10.8	1.30 (1.00, 1.69)
M47	Spondylosis	13.8	12.2	1.13 (0.86, 1.47)
R10	Abdominal and pelvic pain	13.3	11.4	1.17 (0.89, 1.53)
M17	Osteoarthritis of knee	13.3	10.1	1.31 (1.00, 1.73)
N39	Other disorders of urinary system	13.0	9.4	1.38 (1.04, 1.82) [b]
K29	Gastritis and duodenitis	12.7	9.7	1.32 (0.99, 1.75)
N95	Menopausal and other perimenopausal disorders	12.5	8.6	1.46 (1.09, 1.94) [b]
J45	Asthma	11.9	7.0	1.70 (1.26, 2.29) [b]
D22	Melanocytic nevi	11.7	9.2	1.28 (0.95, 1.71)
E03	Other hypothyroidism	11.7	9.5	1.23 (0.92, 1.66)
J30	Vasomotor and allergic rhinitis	11.7	8.8	1.32 (0.98, 1.78)
R42	Dizziness and giddiness	11.1	6.0	1.84 (1.35, 2.52) [b]
F43	Reaction to severe stress, and adjustment disorders	10.9	7.0	1.56 (1.15, 2.14) [b]
E14	Unspecified diabetes mellitus	10.9	6.4	1.69 (1.23, 2.31) [b]
A09	Infectious gastroenteritis and colitis, unspecified	10.6	6.3	1.69 (1.23, 2.33) [b]
M79	Other and unspecified soft tissue disorders, not elsewhere classified	10.6	7.2	1.48 (1.08, 2.03) [b]
L30	Other and unspecified dermatitis	10.6	7.3	1.44 (1.05, 1.98) [b]
L30	Personal history of medical treatment	10.6	7.7	1.38 (1.01, 1.89) [b]
Q66	Congenital deformities of feet	10.3	8.0	1.29 (0.94, 1.77)
I83	Varicose veins of lower extremities	10.3	8.8	1.18 (0.86, 1.62)
E79	Disorders of purine and pyrimidine metabolism	10.1	6.8	1.49 (1.08, 2.06) [b]
T78	Adverse events, not elsewhere classified	10.1	5.9	1.71 (1.23, 2.37) [b]

[a]Only comorbidities present in > 10% of PKU patients are shown; a full listing of the top 50 comorbidities is provided in Additional file 1: Table S3
[b]Comorbidities that had a significant PR vs the control population

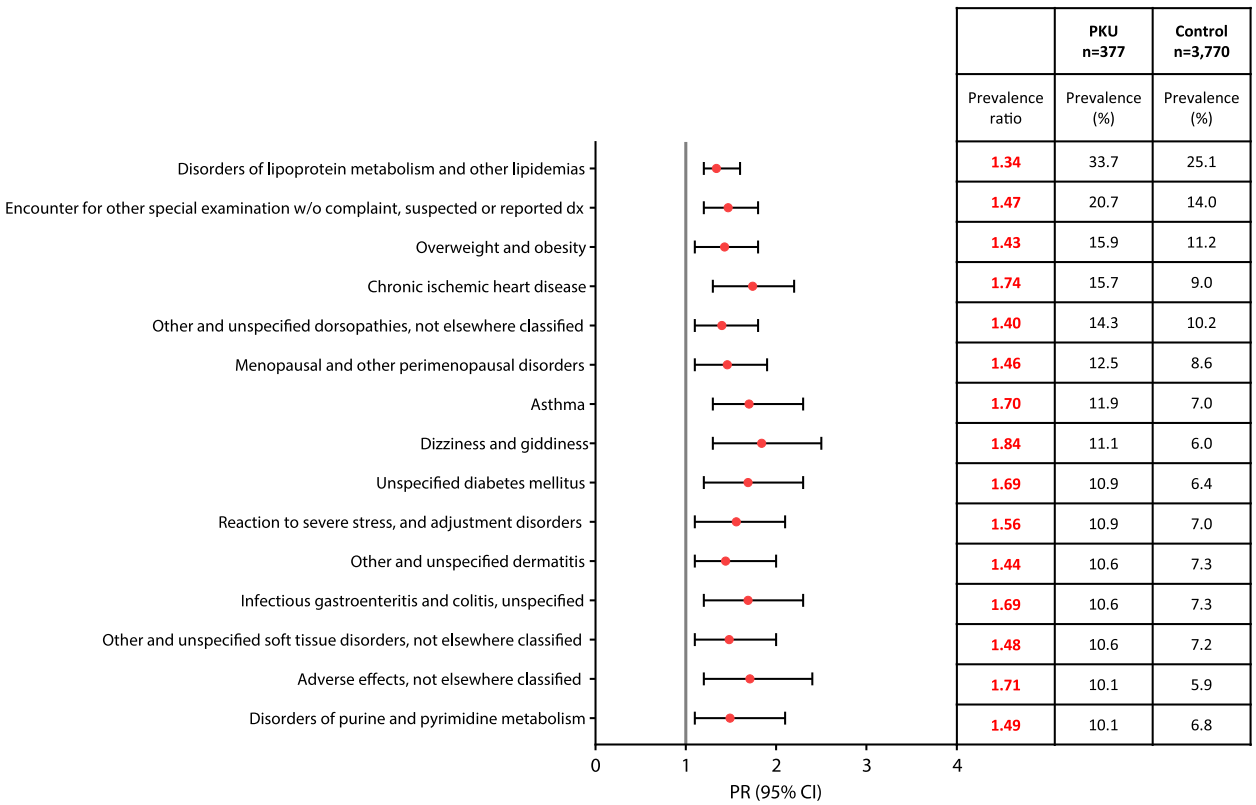

Fig. 1 Comorbidities with a prevalence > 10% among the 50 most frequent that are significantly more prevalent in the PKU vs control population

specified examinations without complaint, suspected or reported diagnosis (Prevalence = 23.6%; PR = 1.52; 95% CI 1.13–2.05); infectious gastroenteritis and colitis (Prevalence = 14.9%; PR = 1.51; 95% CI 1.01–2.25); reaction to severe stress and adjustment disorders (Prevalence = 13.7%, PR = 1.7; 95% CI 1.14–2.67); overweight and obesity (Prevalence = 11.8%; PR = 1.7; 95% CI 1.05–2.63); other and unspecified soft tissue disorders, not elsewhere classified (Prevalence = 11.2%, PR = 2.0; 95% CI 1.27–3.31); and unspecified and other anxiety disorders (Prevalence = 10.6%; PR = 2.0; 95% CI 1.22–3.28). A complete list of the 50 most prevalent comorbidities among early-diagnosed PKU patients is provided in Additional file 1: Table S5.

Among the remainder of the top 50 comorbidities (Additional file 1: Table S5), those with a significant PR > 1.5 for the early-diagnosed PKU population vs matched controls were: hypotension (Prevalence = 6.2%; PR = 2.78; 95% CI 1.40–5.49); encounter for other consultation and medical advice (Prevalence = 6.8%; PR = 2.3; 95% CI 1.24–4.42); thoracic, thoracolumbar, and lumbosacral intervertebral disc disorders (Prevalence = 7.5%; PR = 2.2; 95% CI 1.19–3.99); major depressive disorder, recurrent (Prevalence = 6.8%: PR = 2.1; 95% CI 1.11–3.89); dizziness and giddiness (Prevalence = 6.2%; PR = 2.0; 95% CI 1.05–3.95); scoliosis (Prevalence = 6.8; PR = 2.0; 95% CI 1.09–3.82); disorders of lipoprotein metabolism and other lipidemias (Prevalence = 8.7%; PR = 1.8; 95% CI 1.07–3.18); need for immunization against combinations of infectious diseases (Prevalence = 8.1%; PR = 1.8; 95% CI 1.01–3.14); and acute tonsillitis (Prevalence = 9.9%; PR = 1.7; 95% CI 1.03–2.82).

The most common ATC categories of prescribed agents that are significantly more prevalent in early-diagnosed PKU population vs controls are (Table 6): nervous system (26.7% vs 17.8%; PR 1.50; 95% CI 1.14, 1.98), alimentary tract and metabolism (24.8% vs 14.0%; PR 1.78; 95% CI 1.32, 2.39), and cardiovascular (12.4% vs 6.3%; PR 1.98; 95% CI 1.26, 3.11). The ATC subcodes for the prescribed agents with significant differences between the early-diagnosed and control populations are for acid-related disorders (16.1% vs 9.3%; PR 1.73; 95% CI 1.18, 2.54), systemic corticosteroids (6.8% vs 3.4%; PR 2.00; 95% CI 1.07, 3.74), vitamins (5.6% vs 0.6%; PR 9.0; 95% CI 3.71, 21.8), and diuretics (3.1% vs 0.3%; PR 10.0; 95% CI 2.93, 34.18). A full listing of the top 50 ATC codes is provided in Additional file 1: Table S6.

Late-diagnosed adult PKU patients

All of the 50 most frequent comorbidities were present in > 10% of the adult late-diagnosed PKU patients (Table 7).

Table 4 ATC codes of the top 50 most commonly prescribed agents in the PKU population[a]

ATC code or subcode	Category or subcategory	PKU patients ($n = 377$) %	Control group ($n = 3,770$) %	PR (95% CI)
C	**Cardiovascular system**	**43.8**	**37.4**	**1.17 (1.04, 1.32)** [b]
C09	Agents acting on the renin-angiotensin system	30.0	27.0	1.11 (0.94, 1.31)
C07	Beta blocking agents	24.9	19.9	1.25 (1.04, 1.51) [b]
C10	Lipid modifying agents	19.4	13.1	1.48 (1.19, 1.85) [b]
C03	Diuretics	15.9	10.4	1.53 (1.19, 1.97) [b]
C08	Calcium channel blockers	12.5	8.9	1.40 (1.05, 1.86) [b]
C01	Cardiac therapy	6.1	3.1	1.95 (1.26, 3.01) [b]
A	**Alimentary tract and metabolism**	**40.6**	**29.6**	**1.37 (1.20, 1.56)** [b]
A02	Drugs for acid related disorders	29.4	20.2	1.46 (1.23, 1.72) [b]
A11	Vitamins	4.5	2.0	2.27 (1.35, 3.80) [b]
A12	Minerals	3.7	1.3	2.86 (1.59, 5.13) [b]
N	**Nervous system**	**40.3**	**28.4**	**1.42 (1.24, 1.62)** [b]
N02	Analgesics	24.4	19.0	1.28 (1.06, 1.55) [b]
N06	Psychoanaleptics	17.2	9.5	1.82 (1.43, 2.31) [b]
N05	Psycholeptics	8.8	5.4	1.62 (1.14, 2.30) [b]
N03	Antiepileptics	5.3	2.9	1.82 (1.14, 2.89) [b]
N07	Other nervous system drugs	2.7	1.3	2.08 (1.06, 4.08) [b]
J	**Antiinfectives for systemic use**	**36.6**	**34.0**	**1.08 (0.94, 1.24)**
J01	Antibacterials for systemic use	34.7	32.8	1.06 (0.92, 1.23)
J07	Vaccines	1.9	0.3	6.36 (2.48, 16.32) [b]
M	**Musculo-skeletal system**	**35.3**	**32.0**	**1.10 (0.95, 1.27)**
M01	Antiinflammatory and antirheumatic products	29.4	27.5	1.07 (0.91, 1.26)
M04	Antigout preparations	7.7	4.9	1.58 (1.09, 2.31) [b]
H	**Systemic hormonal preparations, excl. Sexual hormones and insulins**	**24.7**	**20.6**	**1.20 (0.99, 1.44)**
H03	Thyroid therapy	16.7	15.3	1.09 (0.86, 1.39)
H02	Corticosteroids for systemic use	10.3	6.9	1.51 (1.09, 2.07) [b]
D	**Dermatologicals**	**22.0**	**15.6**	**1.41 (1.15, 1.73)** [b]
D07	Corticosteroid, dermatological preparations	12.5	9.0	1.39 (1.04, 1.85) [b]
D01	Antimycotics for dermatological use	5.6	3.5	1.58 (1.01, 2.47) [b]
R	**Respiratory system**	**21.5**	**16.6**	**1.30 (1.06, 1.59)** [b]
R03	Drugs for obstructive airway diseases	13.0	9.8	1.32 (1.00, 1.74)
G	**Genitourinary system and sexual hormones**	**17.2**	**11.6**	**1.49 (1.17, 1.89)** [b]
G01	Gynecological antiinfectives and antiseptics	3.2	1.4	2.31 (1.24, 4.28) [b]
B	**Blood and blood forming organs**	**16.2**	**14.5**	**1.12 (0.88, 1.42)**
B01	Antithrombotic agents	13.3	12.0	1.10 (0.84, 1.45)
S	**Sensory organs**	**8.8**	**11.4**	**0.77 (0.55, 1.08)**

[a]Data are only shown for subcodes that were prescribed in > 10% of PKU patients or those that were significant vs the control population. ATC category totals may not add up because subcategories with < 5 patients in the PKU group have been excluded from the table, but may still count to the total for the ATC class of drug

[b]ATC codes that had a significant PR vs the control population

One letter ATC codes (e.g. Dermatologicals, Cardiovascular system) are shown in bold

The most frequent recorded ICD-10-GM codes were essential primary hypertension (Prevalence = 61.1%), disorders of lipoprotein metabolism and other lipidemias (Prevalence = 52.3%), and dorsalgia (Prevalence = 42.1%). Disorders of lipoprotein metabolism and other lipidemias were significantly more prevalent in the late-diagnosed PKU population vs controls (PR = 1.30; 95% CI 1.13–1.49).

Table 5 Comorbidity profile[a] of early-diagnosed adult PKU patients in 2015 in Germany

ICD-10-GM code	Comorbidity	Early-diagnosed PKU population ($n = 161$) %	Control population ($n = 1,610$) %	PR (95% CI)
Z30	Encounter for contraceptive management	46.6	42.4	1.10 (0.92, 1.31)
Z12	Encounter for screening for malignant neoplasms	35.4	30.1	1.18 (0.94, 1.47)
N89	Other noninflammatory disorders of vagina	31.7	27.8	1.14 (0.90, 1.45)
J06	Acute upper respiratory infections of multiple and unspecified sites	29.2	27.6	1.06 (0.82, 1.36)
M54	Dorsalgia	26.1	22.6	1.15 (0.88, 1.52)
Z01	Encounter for other specified exam without complaint, suspected or reported dx	23.6	15.5	1.52 (1.13, 2.05) [b]
N94	Pain and other condition associated with female genital organs and menstrual cycle	18.0	12.9	1.39 (0.98, 1.98)
R10	Abdominal and pelvic pain	15.5	13.0	1.19 (0.81, 1.74)
J30	Vasomotor and allergic rhinitis	14.9	11.4	1.30 (0.88, 1.93)
A09	Infectious gastroenteritis and colitis, unspecified	14.9	9.9	1.51 (1.01, 2.25) [b]
N92	Excessive, frequent and irregular menstruation	14.3	10.7	1.34 (0.89, 2.00
F43	Reaction to severe stress, and adjustment disorders	13.7	7.8	1.75 (1.14, 2.67) [b]
H52	Disorders of refraction and accommodation	13.0	10.8	1.21 (0.79, 1.84)
F45	Somatoform disorders	13.0	9.3	1.40 (0.91, 2.15)
F32	Major depressive disorder, single episode	12.4	9.9	1.25 (0.81, 1.93)
E66	Overweight and obesity	11.8	7.1	1.67 (1.05, 2.63) [b]
M79	Other and unspecified soft tissue disorders, not elsewhere classified	11.2	5.5	2.05 (1.27, 3.31) [b]
F41	Other anxiety disorders	10.6	5.3	2.00 (1.22, 3.28) [b]
M99	Biomechanical lesions, not elsewhere classified	10.6	8.7	1.21 (0.75, 1.96)
T78	Adverse effects, not elsewhere classified	10.6	6.8	1.56 (0.96, 2.53)
D22	Melanocytic nevi	10.6	8.9	1.19 (0.74, 1.91)

[a] Only comorbidities present in > 10% of PKU Patients are shown; a full listing of the top 50 comorbidities is provided in Additional file 1: Table S5
[b] Comorbidities that had a significant PR vs the control population

Among the 50 most frequent comorbidities, those with a significant PR > 1.5 vs the matched control population are chronic ischemic heart disease (Prevalence = 25.9%; PR = 1.7; 95% CI 1.13–2.13), unspecified diabetes mellitus (Prevalence = 18.5%; PR = 1.7; 95% CI 1.28–2.35), disorders of purine and pyrimidine metabolism (Prevalence = 17.6%; PR = 1.6; 95% CI 1.16–2.17), other chronic obstructive pulmonary disease (Prevalence = 16.2%; PR = 2.0; 95% CI 1.41–2.75), dizziness and giddiness (Prevalence = 14.8%; PR = 1.8; 95% CI 1.26–2.53), atherosclerosis (Prevalence = 13.9%, PR = 1.8; 95% CI 1.26–2.61), asthma (Prevalence = 13.4%; PR = 1.9; 95% CI 1.33–2.81), heart failure (Prevalence = 13.4%; PR = 1.6; 95% CI 1.12–2.32), chronic kidney disease (Prevalence = 13.0%; PR = 1.6; 95% CI1.13–2.38), and other acquired deformities of limbs (Prevalence = 13.0%; PR = 2.6; 95% CI 1.75–3.83). A complete list of the 50 most prevalent comorbidities of the late-diagnosed PKU cohort and the corresponding prevalence in the control cohort is provided in Additional file 1: Table S7.

The most common ATC categories of prescribed agents that are significantly more prevalent in late-diagnosed PKU population vs controls (Table 8) are alimentary tract and metabolism (52.3% vs 41.3%; PR 1.27; 95% CI 1.10, 1.45), nervous system (50.5% vs 36.3%; PR 1.39; 95% CI 1.20, 1.60), and dermatologicals (28.7% vs 18.8%; PR 1.53; 95% CI 1.22, 1.92). The most common ATC subcodes for the prescribed agents with significant differences between the late-diagnosed and control populations are for beta-blockers (39.4% vs 32.6%; PR 1.21; 95% CI 1.01, 1.44), acid-related disorders (39.4% vs 28.3%; PR 1.39; 95% CI 1.16, 1.66), analgesics (33.3% vs 24.8%; PR 1.35; 95% CI 1.10, 1.65), and lipid-modifying agents (32.4% vs 22.5%; PR 1.44; 95% CI 1.17, 1.77). Additionally, diuretics, pyschoanaleptics, antigout preparations, corticosteroids for systemic use, corticosteroid dermatological preparations, antimycotics for dermatological use, drugs for obstructive airway diseases, and gynecological antiinfectives and antiseptics were all prescribed significantly more often in the late-diagnosed vs control populations. The 50 most

Table 6 Top 50 most commonly prescribed ATC codes in the early-diagnosed PKU population[a]

ATC code or subcode	Category or subcategory	Early-diagnosed PKU patients ($n = 161$) %	Control group ($n = 1,610$) %	PR (95% CI)
J	**Antiinfectives for systemic use**	**34.8**	**34.7**	**1.00 (0.80, 1.25)**
J01	Antibacterials for systemic use	32.9	33.9	0.97 (0.77, 1.22)
N	**Nervous system**	**26.7**	**17.8**	**1.50 (1.14, 1.98)** [b]
N06	Psychoanaleptics	14.3	6.1	2.35 (1.54, 3.59) [b]
N02	Analgesics	12.4	11.3	1.10 (0.71, 1.69)
N05	Psycholeptics	8.7	2.2	3.89 (2.14, 7.06) [b]
N03	Antiepileptics	3.7	0.7	5.00 (1.90, 13.14) [b]
M	**Musculo-skeletal system**	**25.5**	**22.5**	**1.13 (0.86, 1.50)**
M01	Antiinflammatory and antirheumatic products	24.8	21.6	1.15 (0.86, 1.53)
A	**Alimentary tract and metabolism**	**24.8**	**14.0**	**1.78 (1.32, 2.39)** [b]
A02	Drugs for acid related disorders	16.1	9.3	1.73 (1.18, 2.54) [b]
A11	Vitamins	5.6	0.6	9.00 (3.71, 21.83) [b]
H	**Systemic hormonal preparations, excl. Sexual hormones and insulins**	**16.8**	**12.7**	**1.32 (0.91, 1.90)** [b]
H03	Thyroid therapy	12.4	9.4	1.32 (0.86, 2.05)
H02	Corticosteroids for systemic use	6.8	3.4	2.00 (1.07, 3.74) [b]
R	**Respiratory system**	**15.5**	**15.1**	**1.03 (0.70, 1.50)**
D	**Dermatologicals**	**13.0**	**11.3**	**1.15 (0.76, 1.76)**
C	**Cardiovascular system**	**12.4**	**6.3**	**1.98 (1.26, 3.11)** [b]
C03	Diuretics	3.1	0.3	10.00 (2.93, 34.18) [b]
G	**Genitourinary system and sexual hormones**	**11.8**	**7.7**	**1.53 (0.97, 2.41)**
B	**Blood and blood forming organs**	**7.5**	**3.5**	**2.11 (1.15, 3.84)** [b]
L	**Antineoplastic and immunomodulating agents**	**4.3**	**1.6**	**2.80 (1.23, 6.37)** [b]

[a]Data are only shown for subcodes that were prescribed in > 10% of PKU patients or those that were significant vs the control population. ATC category totals may not add up because subcategories with < 5 patients in the PKU group have been excluded from the table, but may still count to the total for the ATC class of drug

[b]ATC codes that had a significant PR vs the control population

One letter ATC codes (e.g. Dermatologicals, Cardiovascular system) are shown in bold

frequently prescribed agents in late-diagnosed PKU patients are provided in full in Additional file 1: Table S8.

Discussion

This study was designed to generate additional insights into the clinical burden of adult patients with PKU in Germany compared with the general population.

The unbiased design of this study, only selecting the 50 most common comorbidities and comedications in the PKU population and comparing with a rigorously matched control population, showed several surprising results. While the presence of neuropsychological conditions (e.g. depression and anxiety) at a higher prevalence in the PKU vs control population was to be expected in this analysis, the high prevalence of cardiovascular risk factors/conditions in the PKU population was unexpected. More than a third of adult PKU patients suffered from essential primary hypertension and disorders of lipoprotein metabolism and other lipidemias, while more than 10% had chronic ischemic heart disease, unspecified diabetes mellitus, or obesity. Furthermore, in all of these conditions, except primary hypertension, there was a significantly higher prevalence in the overall PKU population vs matched controls. It is worth noting that several of these conditions are components of metabolic syndrome [13].

The higher comorbid burden in PKU patients is also supported by the significantly higher proportion of patients with CCI scores ≥3 compared with the control population. Indeed, several comorbidities that contribute to the CCI score (e.g. diabetes mellitus, chronic kidney disease [CKD], chronic obstructive pulmonary disease) were found to be significantly more prevalent in the overall PKU population, early-diagnosed PKU population and late-diagnosed PKU population vs controls.

The observed difference in the prevalence of cardiovascular risk factors and diseases is reflected in the pattern of prescribed agents in this PKU population: 43.8% of the PKU population were receiving cardiovascular

Table 7 Comorbidity profile of late-diagnosed adult PKU patients in 2015 in Germany

ICD-10-GM code	Description	Late-diagnosed PKU patients ($n = 216$) %	Control group ($n = 2,160$) %	PR (95% CI)
I10	Essential (primary) hypertension	61.1	58.4	1.05 (0.94, 1.17)
E78	Disorders of lipoprotein metabolism and other lipidemias	52.3	40.4	1.30 (1.13, 1.49) [a]
M54	Dorsalgia	42.1	36.1	1.17 (0.99, 1.38)
H52	Disorders of refraction and accommodation	38.0	33.1	1.15 (0.96, 1.37)
Z12	Encounter for screening for malignant neoplasms	28.2	30.0	0.94 (0.75, 1.18)
I25	Chronic ischemic heart disease	25.9	15.6	1.67 (1.30, 2.13) [a]
E11	Type 2 diabetes mellitus	25.5	19.6	1.30 (1.02, 1.65) [a]
Z25	Need for immunization against other single viral diseases	22.2	20.4	1.09 (0.84, 1.42)
M17	Osteoarthritis of knee	21.3	17.2	1.24 (0.94, 1.63)
Z00	Encounter for general exam without complaint, suspected or reported dx	20.8	20.2	1.03 (0.79, 1.36)
N95	Menopausal and other perimenopausal disorders	20.4	14.5	1.40 (1.06, 1.86) [a]
E04	Other nontoxic goiter	19.9	14.7	1.35 (1.02, 1.80) [a]
M47	Spondylosis	19.4	18.8	1.03 (0.78, 1.37)
E66	Overweight and obesity	19.0	14.2	1.34 (0.99, 1.79)
F32	Major depressive disorder, single episode	19.0	15.8	1.20 (0.90, 1.61)
M53	Other and unspecified dorsopathies, not elsewhere classified	19.0	12.6	1.51 (1.12, 2.03) [a]
Z01	Encounter for other specified exam without complaint, suspected or reported dx	18.5	12.9	1.43 (1.06, 1.94) [a]
E14	Unspecified diabetes mellitus	18.5	10.7	1.73 (1.28, 2.35) [a]
E79	Disorders of purine and pyrimidine metabolism	17.6	11.1	1.59 (1.16, 2.17) [a]
N39	Other disorders of urinary system	17.6	12.5	1.40 (1.03, 1.91) [a]
Z92	Personal history of medical treatment	17.1	13.0	1.32 (0.97, 1.81)
F45	Somatoform disorders	17.1	14.3	1.20 (0.88, 1.64)
J44	Other chronic obstructive pulmonary disease	16.2	8.2	1.97 (1.41, 2.75) [a]
J06	Acute upper respiratory infections of multiple and unspecified sites	15.7	12.2	1.29 (0.93, 1.79)
K29	Gastritis and duodenitis	15.7	11.1	1.42 (1.02, 1.98) [a]
R42	Dizziness and giddiness	14.8	8.3	1.79 (1.26, 2.53) [a]
I83	Varicose veins of lower extremities	14.8	13.0	1.14 (0.82, 1.60)
Z96	Presence of other functional implants	14.4	14.7	0.97 (0.69, 1.37)
N89	Other noninflammatory disorders of vagina	14.4	10.6	1.35 (0.96, 1.92)
M19	Other and unspecified osteoarthritis	14.4	10.1	1.42 (1.00, 2.01)
H35	Other retinal disorders	13.9	11.3	1.23 (0.86, 1.75)
L30	Other and unspecified dermatitis	13.9	9.0	1.54 (1.08, 2.20) [a]
I70	Atherosclerosis	13.9	7.6	1.82 (1.26, 2.61) [a]
J45	Asthma	13.4	6.9	1.93 (1.33, 2.81) [a]
I50	Heart failure	13.4	8.3	1.61 (1.12, 2.32) [a]
M21	Other acquired deformities of limbs	13.0	5.0	2.59 (1.75, 3.83) [a]
E03	Other hypothyroidism	13.0	10.7	1.21 (0.84, 1.75)
N18	Chronic kidney disease	13.0	7.9	1.64 (1.13, 2.38) [a]

Table 7 Comorbidity profile of late-diagnosed adult PKU patients in 2015 in Germany *(Continued)*

ICD-10-GM code	Description	Late-diagnosed PKU patients ($n = 216$) %	Control group ($n = 2,160$) %	PR (95% CI)
N40	Enlarged prostate	13.0	12.3	1.06 (0.73, 1.52)
K76	Other diseases of liver	12.5	10.6	1.18 (0.82, 1.72)
M16	Osteoarthritis of hip	12.5	8.9	1.41 (0.96, 2.05)
H25	Age-related cataract	12.5	11.2	1.12 (0.77, 1.62)
D22	Melanocytic nevi	12.5	9.4	1.34 (0.92, 1.95)
I49	Other cardiac arrhythmias	12.0	10.0	1.20 (0.82, 1.76)
Z95	Presence of cardiac and vascular implants and grafts	12.0	8.1	1.48 (1.00, 2.18)
M51	Thoracic, thoracolumbar, and lumbosacral intervertebral disc disorders	11.6	12.8	0.91 (0.62, 1.33)
R10	Abdominal and pelvic pain	11.6	10.1	1.14 (0.77, 1.69)
M42	Spinal osteochondrosis	11.6	8.5	1.36 (0.92, 2.01)
H61	Other disorders of external ear	11.6	10.5	1.11 (0.75, 1.63)

[a]Comorbidities that had a significant PR vs the control population

medicine vs 37.4% of the control population. Furthermore, beta-blockers, lipid-modifying agents, diuretics, cardiac therapy, and calcium-channel blockers were all prescribed significantly more often in the PKU vs control populations.

Treatments for acid-related disorders were prescribed in > 25% of PKU patients and at a significantly higher level than observed in matched controls, which may be due to the PKU diet.

Our study assessed a prevalence of adult PKU patients in 2015 in Germany (1 in 9,872) that is consistent with the reported prevalence/incidence of PKU among newborns of 1 in 6,000 to 1 in 10,000 live births [14, 15].

Although our analysis is unable to derive information on the degree of blood Phe control or disease severity exhibited by these patients, it is worth noting that < 1.3% of the overall PKU population (< 5 of the 377 PKU patients) were receiving sapropterin (all early-diagnosed patients) and only 13.8% of the overall PKU population were receiving D.A.S., again mainly in the early-diagnosed group (29.2% of early-diagnosed patients vs 2.6% of the late-diagnosed patients). This may indicate that relatively few of the late-diagnosed patients are well-controlled or on-diet vs the early-diagnosed patients.

When we consider the early-diagnosed population, they have a higher likelihood of their condition being continuously managed from an early age, they are relatively younger adults (mean age 30.7 years), and approximately 30% of them are receiving D.A.S. as part of their PKU management regime. Despite this, more than 10% of the population have an ICD code for conditions such as overweight and obesity (11.8%), other anxiety disorders (10.6%), and reaction to severe stress and adjustment disorders (13.7%). Furthermore, several conditions are significantly more prevalent in the early-diagnosed PKU population vs age-matched control subjects, including hypotension (PR 2.78), major depressive episodes (PR = 2.1), and disorders of lipid metabolism and other lipidemias (PR = 1.8).

The etiology of the comorbidities identified in this study cannot be ascertained from this type of study, but several interesting hypotheses can be generated based on knowledge of the underlying condition and the associated dietary management.

For instance, the higher level of risk for chronic ischemic heart disease in late-diagnosed PKU patients (Prevalence = 15.7%; PR = 1.7; 95% CI 1.30–2.13) could be associated with the higher prevalence of disorders of lipoprotein metabolism in this cohort (Additional file 1: Table S7) or several cardiometabolic anomalies that have been previously identified in PKU patients. Several published studies identify an increased or reduced risk of atherosclerosis or associated cardiovascular risk factors in PKU patients.

A recent study [16] demonstrated increased aortic stiffness in PKU patients ($n = 41$, 6 to 50 years of age), measured by applanation tonometry, when compared with a matched healthy control group and this was associated with higher Phe levels. However, another study [17] did not identify any difference in arterial stiffness or carotid intima media thickness (a surrogate marker of atherosclerosis) between PKU patients ($n = 43$, mean age 28.1 [SD 0.96]) and non-PKU control subjects ($n = 58$).

A correlation between elevated blood Phe levels and increased blood pressure has been demonstrated [18] in a study of 141 patients (6 months to 50 years of age) with classical PKU ($n = 66$; blood Phe ≥1200 μmol/L), mild-moderate PKU ($n = 34$; blood Phe 360–1200 μmol/L), or

Table 8 ATC code and subcode of the top 50 most commonly prescribed agents in the late-diagnosed PKU population[a]

ATC code or subcode	Category or subcategory	Late-diagnosed PKU patients ($n = 216$) %	Control group ($n = 2,161$) %	PR (95% CI)
C	**Cardiovascular system**	**67.1**	**60.6**	**1.11 (1.00, 1.22)**
C09	Agents acting on the renin-angiotensin system	47.7	44.7	1.07 (0.92, 1.24)
C07	Beta blocking agents	39.4	32.6	1.21 (1.01, 1.44) [b]
C10	Lipid modifying agents	32.4	22.5	1.44 (1.17, 1.77) [b]
C03	Diuretics	25.5	17.9	1.42 (1.11, 1.82) [b]
C08	Calcium channel blockers	19.9	15.1	1.32 (0.99, 1.76)
C01	Cardiac therapy	10.2	5.4	1.90 (1.23, 2.93) [b]
A	**Alimentary tract and metabolism**	**52.3**	**41.3**	**1.27 (1.10, 1.45)** [b]
A02	Drugs for acid related disorders	39.4	28.3	1.39 (1.16, 1.66) [b]
A10	Antidiabetics	15.7	13.4	1.17 (0.85, 1.63)
N	**Nervous system**	**50.5**	**36.3**	**1.39 (1.20, 1.60)** [b]
N02	Analgesics	33.3	24.8	1.35 (1.10, 1.65) [b]
N06	Psychoanaleptics	19.4	12.0	1.62 (1.20, 2.17) [b]
M	**Musculo-skeletal system**	**42.6**	**39.2**	**1.09 (0.92, 1.28)**
M01	Antiinflammatory and antirheumatic products	32.9	31.9	1.03 (0.84, 1.26)
M04	Antigout preparations	13.0	8.3	1.56 (1.08, 2.27) [b]
M05	Drugs for treatment of bone diseases	3.7	2.6	1.43 (0.69, 2.96)
J	**Antiinfectives for systemic use**	**38.0**	**33.5**	**1.13 (0.95, 1.36)**
J01	Antibacterials for systemic use	36.1	32.0	1.13 (0.93, 1.36)
H	**Systemic hormonal preparations, excl. Sexual hormones and insulins**	**30.6**	**26.5**	**1.15 (0.93, 1.43)**
H03	Thyroid therapy	19.9	19.7	1.01 (0.76, 1.34)
H02	Corticosteroids for systemic use	13.0	9.4	1.37 (0.95, 1.99)
D	**Dermatologicals**	**28.7**	**18.8**	**1.53 (1.22, 1.92)** [b]
D07	Corticosteroid, dermatological preparations	16.2	11.2	1.45 (1.05, 2.01) [b]
D01	Antimycotics for dermatological use	7.9	4.7	1.68 (1.03, 2.76) [b]
R	**Respiratory system**	**25.9**	**17.6**	**1.47 (1.15, 1.87)** [b]
R03	Drugs for obstructive airway diseases	18.1	11.8	1.53 (1.13, 2.08) [b]
B	**Blood and blood forming organs**	**22.7**	**22.6**	**1.00 (0.77, 1.30)**
B01	Antithrombotic agents	20.4	19.7	1.03 (0.78, 1.36)
G	**Genitourinary system and sexual hormones**	**21.3**	**14.4**	**1.47 (1.12, 1.94)** [b]
G04	Urologicals	12.0	8.6	1.40 (0.95, 2.06)
G01	Gynecological antiinfectives and antiseptics	3.2	0.6	5.38 (2.17, 13.35) [b]
S	**Sensory organs**	**10.6**	**14.4**	**0.74 (0.50, 1.11)**

[a]Data are only shown for subcodes that were prescribed in > 10% of PKU patients or those that were significant vs the control population. ATC category totals may not add up because subcategories with < 5 patients in the PKU group have been excluded from the table, but may still count to the total for the ATC class of drug

[b]ATC codes that had a significant PR vs the control population

One letter ATC codes (e.g. Dermatologicals, Cardiovascular system) are shown in bold

mild hyperphenylalaninemia ($n = 41$; MHPA; blood Phe 120–360 μmol/L). Patients with PKU ($n = 100$) had higher blood pressure than those with MHPA .

In contrast to the identified risk for ischemic heart diseases, lower levels of LDL cholesterol have been observed in adults with PKU, which may be simply due to the PKU diet or possibly via a direct effect of high blood Phe levels on cholesterol synthesis [19]. Another study [18] demonstrated that although total and LDL cholesterol were lower in classical PKU vs MHPA patients, lipid markers

seemed to correlate with adherence to a PKU diet, as they were lower in treated PKU patients vs untreated or less stringently treated PKU patients. This may indicate that, regardless of the severity of PKU, lipid markers could be improved by adherence to diet. Of note, overweight or obese PKU patients in this study exhibited an atherogenic lipid profile (elevated levels of triglycerides, total cholesterol, LDL cholesterol and reduced levels of high-density lipoprotein [HDL] cholesterol), in addition to elevated levels of high sensitivity C-reactive protein (hsCRP).

Another study [20] in 59 patients with PKU and 44 healthy controls (11 to 17 years of age) found significantly lower levels of cardioprotective HDL cholesterol in well-controlled ($n = 24$; blood Phe < 360 μmol/L) vs poorly-controlled ($n = 35$; blood Phe > 360 μmol/L) PKU patients; both groups were significantly lower than non-PKU controls. Additionally, higher levels of homocysteine and increased mean platelet volume levels were also observed in PKU patients vs healthy controls and differences in these parameters were more evident in poorly-controlled PKU patients [20].

In summary, there is no consistent evidence that PKU patients may be at a higher risk for developing atherosclerosis. However, all of the cited studies were performed in relatively young PKU patients, and therefore, the effect of chronic, longer-term exposure to elevated blood Phe or the PKU diet could not be assessed. Our study provides a snapshot of the comorbidities present in an older population (late-diagnosed) of patients with PKU and demonstrated a significant PR vs controls for both risk factors (disorders of lipoprotein metabolism and other lipidemias) and cardiovascular disease (chronic ischemic heart disease and atherosclerosis). Further studies in older populations of PKU patients are required to confirm this association and elucidate the etiology.

An increased risk for being overweight or having obesity in dietary treated PKU patients, as found in early-diagnosed PKU patients in our study (Prevalence = 11.8; PR = 1.7; 95% CI 1.05–2.63), has been widely discussed in a review by Rocha et al. [21], although it could not be ascertained if weight issues were a result of the underlying condition (PKU), a consequence of treatment (PKU diet), or due to inadequate metabolic control. A study of 236 patients with PKU (mean age 26 [SD 7] years) proposed that an increased proportion of obese individuals may simply reflect the trends seen in the general population, but they did find a correlation between increasing body mass index (BMI) and higher blood Phe concentrations [22].

A study of BMI data from 947 patients with PKU (1.7 months to 26 years) found that in both children and adults with PKU (< 18 and > 19 years of age, respectively), females appear particularly vulnerable to excess weight gain and this may lead to a higher risk of atherosclerosis in PKU patients [23]. In our study, only early-diagnosed PKU patients showed a tendency to be overweight/obese compared with the control group. However, we do not know the proportion of PKU patients that were following a PKU diet or the degree of blood Phe control/lack of Phe control. However, we do know that approximately 98 and 70% of late- and early-diagnosed patients, respectively, were not receiving D.A.S.

In our study, both unspecified diabetes mellitus (Prevalence = 18.5; PR = 1.7; 95% CI 1.28–2.35) and type 2 diabetes mellitus (Prevalence 25.5; PR = 1.3: 95% CI 1.02–1.65) were more prevalent in late-diagnosed PKU patients vs control subjects. In addition to being a serious chronic condition, diabetes is also a significant risk factor for both cardiovascular and renal disease. Given these findings, the management of these patients may need to include assessment of insulin levels and the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) index.

Because of the high carbohydrate intake inherent in the PKU diet, there has been copious discussion regarding an increased risk of diabetes in these patients. However, there is currently no clear evidence that patients with PKU exhibit a higher risk of developing diabetes and most studies only include children or young adults, which may exclude the development timeline of type 2 diabetes mellitus.

It is interesting to note that several of the conditions identified among PKU patients in this study (diabetes mellitus, dyslipidemia, obesity) are constituents of the metabolic syndrome. Kanufre et al. [24] found that overweight PKU patients may be vulnerable to the development of the metabolic syndrome.

Our study includes patients aged 18–92 years and therefore includes older age groups, especially in the late-diagnosed population (range 46–96 years), that are not represented in published studies addressing cardiometabolic comorbidities in adults with PKU. Studies are required assessing the long-term effect of various atherogenic factors like obesity, diabetes mellitus, hypertension, oxidative stress and other factors which may not be evident in younger patient populations. Many of the late-diagnosed PKU patients (median age 65 years in our study) may be in institutions or nursing homes. It is well known that patients living in institutions have a lower life expectancy [25]. Findings indicate that the mean prevalence of heart failure is 20% (range 15–45%) and that there is a significant level of comorbidity (dementia, diabetes mellitus, and chronic obstructive pulmonary disease) in nursing home residents with heart failure [26, 27].

The finding that late-diagnosed PKU patients exhibit a higher prevalence of CKD compared with their matched controls (Prevalence = 13.0%; PR = 1.6; 95% CI 1.13–2.38) is an interesting finding and there is evidence to suggest that the PKU diet also may be a factor. In a well-controlled

study analyzing renal function in 67 patients with PKU, Hennermann et al. [28] demonstrated that 19% of PKU patients had impaired renal function, 31% had proteinuria, and 23% had arterial hypertension. Furthermore, renal function declined with increasing protein intake. The authors propose a negative impact of amino acid supplementation on renal function, but additional studies are required to confirm these findings.

There is a plethora of evidence supporting the role of oxidative stress as an underlying factor in the etiology of several diseases, including atherosclerosis, chronic kidney disease, and diabetes (for review see Liguori et al. [29]). The evidence for increased levels of oxidative stress in PKU patients and the role it plays in PKU has been previously discussed [30, 31].

Preissler et al. [32] found that oxidative stress is induced in cultured astrocytes by concentrations of Phe normally found in PKU patients and that this may lead to cell death. Two studies have found evidence of increased oxidative stress in PKU patients [33, 34] that was associated with increased levels of DNA or tissue damage, even in well-controlled PKU patients. In summary, increased oxidative stress in PKU patients is evident; however, there are no rigorous studies investigating if this translates into a higher risk of atherosclerosis or other diseases in PKU patients.

The results of a similar study were recently published by Burton et al. [35]; the identified comorbidities among PKU patients in the US show some similarities to those present in the German PKU patients. Although a direct comparison of the two populations may be limited - e.g. the study compared the prevalence of comorbidities selected by an expert panel of physicians (rather than the most prevalent comorbidities), used the ICD-9 coding (rather than ICD-10) and the US population was made up of younger patients (mean age approximately 35 years), mostly born after the start of NBS - similar PR's were found for several comorbidities including overweight and obesity, gastrointestinal disorders, and asthma. One may speculate that this is due to the Phe-restricted diet featuring high amounts of amino acid supplements, which may contribute to the presence of oesophagitis and gastroesophageal reflux. On the other hand, an increased prevalence of cardiovascular diseases was not found in the US investigation, which is likely due to the lower age of patients. In the US study, renal insufficiency (both with and without hypertension) and calculus of the kidney were identified as significantly more prevalent in the PKU vs control population. Although our study identified a significant PR for CKD in the late-diagnosed population vs controls, renal insufficiency and renal complications were not among the top 50 comorbidities in the early-diagnosed population, who are more comparable to the US study population (average age 31 vs 35 years). This may be due to the different approaches to treatment; only 2.6% of the late-diagnosed group and 29.2% of the early-diagnosed group in Germany are prescribed amino acid supplements. In the study by Hennermann et al. [28], it was hypothesized that renal excretion of amino acids may be responsible for renal damage. It is also of note that several comorbidities that may be amenable to prevention (e.g. obesity, hypertension, dyslipidemia) are more prevalent in the early-treated population vs their controls, as well as in the late-treated population. While this may be expected in the late-treated population, the presence of these comorbidities in the early-treated population may reflect the focus of care (i.e. control of blood Phe and diet) in patients with PKU and that assessment/management of these comorbidities may need to become part of clinical practice.

Strengths and limitations

Claims data analyses are primarily collected for reimbursement purposes and do not necessary cover clinical parameters. Therefore, the study had to rely on the information that is coded in the ICD-10-GM catalog. The ICD-10-GM catalog provides information about the disorders of aromatic amino-acid metabolism, but contains no specific codes for the severity of PKU. Therefore, we may have included patients with a very mild form of PKU, which could result in underestimating the burden of disease for the severe PKU patients.

PKU patients might be screened more frequently, due to their annual (or more frequent) visits to their PKU clinic, leading to a higher rate of detection of comorbidities vs control subjects.

The higher proportion of females in the PKU group, especially in the early-diagnosed population, could be due to the recommendation that females of reproductive age be screened for risks associated with maternal PKU [4].

The stratification of the study population into early-diagnosed and late-diagnosed PKU patients was based exclusively on the year of birth in relation to the implementation of NBS for PKU in Germany during 1969/1970. This approach does not account for patients who were born in 1969/1970 (who may or not have been screened at birth), patients who may have been born in other countries [36], or for patients born before 1969 with older siblings with diagnosed PKU (who were therefore diagnosed at birth).

On the other hand, this study has some major strengths. First, the utilized data source allows generalization of our results to a major part of the German population, as approximately 85% of the German population are covered by statutory health insurance (SHI). In contrast to registries and clinical trials, where a selected population is investigated, this analysis should not be affected by a selection bias. Also, participants of the German SHI system benefit from nearly full coverage of all healthcare

services; minor copayments exist but these are limited to 2% of the annual income of the insured individuals (1% for chronically ill individuals). German claims data therefore provides a near-complete picture of all direct healthcare utilization; therefore, our study should provide a complete picture of comorbidities and any prescribed medications.

Generalizability

The InGef research database is based on claims data from the SHI system, but is adjusted to the German overall population in terms of age and sex. As proportionately more males choose private health insurance in Germany, the proportion of females is higher in the SHI population than in the overall German population; this limits the generalizability of our results. On the other hand, the generalizability of the results to the German population might be biased because individuals with an annual income above a defined threshold could choose a private health insurance instead of the SHI. These individuals tend to be healthier than the individuals that have to be insured by the SHI [37]. Moreover, the prevalence of PKU shows regional differences among the federal states in Germany. The adjusted age and sex distribution of the InGef research database does not account for these regional differences [38].

Conclusions

This retrospective matched cohort analysis using German SHI claims data assessed the clinical burden of PKU in Germany. Adult PKU patients, even those who are early-diagnosed, suffer not only from the direct burden of PKU, but are also likely to present with additional comorbidities, including cardiometabolic risk factors, that impact patients' lives. An increased healthcare burden is reflected by a higher intake of prescriptions of gastrointestinal agents, analgesics and antipyretics, statins, and antidepressants. The matched comparison revealed that PKU patients suffered more often from intellectual, developmental, and psychological disorders and that PKU patients, especially those who are late-diagnosed, have a higher burden of disease compared with the general population. Future studies in adult PKU patients must clarify if these comorbidities, several of which were not expected in this population, are caused by environmental conditions, the underlying disease, or are related to the requisite treatment.

Methods

Study design

This study was designed as a retrospective matched cohort analysis comparing PKU patients with matched controls from the general population. The study utilized German statutory health insurance (SHI) claims data and was conducted from the perspective of the German SHI.

Data source

The Institut für angewandte Gesundheitsforschung Berlin (InGef) research database contains anonymized healthcare claims of approximately four million covered lives. It is adjusted to the overall German population in terms of age and gender and is considered to be in good accordance to the overall German population for measures of morbidity, mortality, and drug usage [39]. The InGef research database includes a geographically well-distributed population from all federal states of Germany, which is insured by approximately 70 different insurance companies. The claims data are regularly audited by the insurance companies for reimbursement purposes and are prepared in accordance with German Social Law (paragraphs 287 SGB V and 75 SGB X). Data on patients and physicians is anonymized, as are the providers and the health insurances, before data is made available to the InGef, ensuring compliance with the strict data protection regulations in Germany.

Study period

The study period was from January 1, 2010 to December 31, 2015. PKU patients were enrolled within this time frame (enrollment period) and the outcomes were analyzed for a 1-year period from January 1, 2015 to December 31, 2015 (outcomes observation period).

Study population

PKU patients were identified using International Statistical Classification of Diseases and Related Health Problems, 10th revision, German Modification (ICD-10-GM) codes (E70.0 [Classical phenylketonuria] or E70.1 [Other hyperphenylalaninemias]) in the inpatient (main or secondary discharge diagnoses) and/or outpatient setting (verified diagnoses) during the enrollment period. They were excluded if they were younger than 18 years of age on January 1, 2015 or if they were lost to follow-up due to a sickness fund switch within the outcomes observation period.

Subgroups

The adult PKU cohort was divided into early-diagnosed and late-diagnosed patients based on their birth year in relation to the implementation of newborn screening (NBS) for PKU in Germany between 1969 and 1970 [40]. Hence, adult PKU patients born prior to 1969 were presumed to be late-diagnosed.

Matching

For each of the eligible adult PKU patients, ten controls were drawn from the InGef research database via direct,

exact matching, without replacement on age and sex. Non-PKU controls (no PKU diagnosis code in the enrollment period) were required to be continuously enrolled in the database during the outcomes observation period, except for patients who died.

Matching balance was measured by the standardized difference with a threshold of 10%, indicating an imbalance of the matching parameters if the standardized difference exceeds the threshold [41–44].

Outcomes

The 50 most common comorbidities among the overall adult PKU cohort, the early-diagnosed PKU cohort, and the late-diagnosed PKU cohort in 2015 were identified and rank-ordered using ICD-10-GM codes and the prevalence of those comorbidities compared with the matched control group. The most commonly prescribed concomitant medications in 2015 were identified using 7-digit Anatomical Therapeutic Chemical (ATC) codes and pharmaceutical central numbers (PZN) and prescribing levels compared with the matched control group. Differences between the groups were tested using 95% confidence intervals (95% CI) of prevalence ratio (PR).

Additionally, the Updated Charlson Comorbidity Index (CCI) was analyzed to measure the overall health status [45]. The CCI is a weighted index that takes into account the number and the seriousness of comorbid diseases by assigning points for certain illnesses. The CCI score is the sum of the points for each disease and higher scores indicate a greater burden of disease; scores run from 0 to 29, but are generally presented categorically as 0, 1, 2, 3 and ≥ 4. Component comorbidities of the CCI are myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, hemiplegia or paraplegia, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, diabetes without chronic complications, diabetes with chronic complications, renal disease, any malignancy (including leukemia and lymphoma), metastatic solid tumor, mild liver disease, moderate or severe liver disease, and acquired immune deficiency syndrome (AIDS)/human immunodeficiency virus (HIV). Differences between groups for CCI scores were tested using a chi-square test and 95% CI of PR.

Additional file

Additional file 1: Tables S1-S8. (DOCX 86 kb)

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Authors' contributions

JA, KK, and CJ analyzed the dataset. All authors interpreted the data. KK and PL were responsible for drafting an initial outline of the manuscript for review by all authors prior to development of a first draft. All authors provided critical review, revision of drafts, and approval of the the final manuscript.

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Availability of data and materials

The utilized database in this study is available from the Intitut für angewandte Gesundheitsforschung Berlin (InGef) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

Ethics approval and consent to participate

This study used anonymized German claims data. Therefore, no ethics approval was needed by an independent ethics committee or institutional review board. The utilized database addresses all data protection regulations in Germany. To ensure the protection of individual data and privacy, regions that are smaller than federal states or patient cohorts with less than 100 individuals were not analyzed in a granular way. Furthermore, patient counts below 5 were reported as "< 5".

Consent for publication

Not applicable.

Competing interests

IA, MJ, AJ, PL, and CS are full-time employees and stockholders of BioMarin Europe Ltd. KK, JA, CJ, and SB are full-time employees of Xcenda, acting as contractors of BioMarin Europe Ltd. for the execution of this study. FT received honoraria for presentations from BioMarin. AM has been a member of scientific advisory boards supported by BioMarin Europe Ltd. and has received honoraria as a speaker for BioMarin Europe Ltd. FR has received speaker and consulting honoraria from BioMarin Europe Ltd.

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Publisher's Note

Modul 3

Health economic burden of patients with phenylketonuria (PKU) – A retrospective study of German health insurance claims data

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Health economic burden of patients with phenylketonuria (PKU) – A retrospective study of German health insurance claims data

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ABSTRACT

This retrospective matched-cohort analysis compared health-economic burdens of adults (≥18 years; $n = 377$) with phenylketonuria (PKU) and age/gender-matched non-PKU controls ($n = 3770$) in Germany. Healthcare costs and resource-utilization were analyzed for the year 2015. Differences between groups were tested using 95% CI of mean differences (MD). PKU patients had significantly higher mean costs in total (MD €3307, 95% CI €1736–€4879), for pharmaceuticals (MD €1912, 95% CI €1195–€2629) [including dietary amino-acid supplements (MD €1268, 95% CI €864–€1672)], and outpatient costs (MD €395, 95% CI €115–€675). Inpatient costs (MD €904, 95% CI -€293 to €2100) and costs for aids and remedies (MD €97, 95% CI -€10 to €203) were also higher in PKU patients. PKU patients had more outpatient visits and stayed longer in hospital. Adult PKU patients incur higher total healthcare costs than non-PKU controls, especially regarding pharmaceuticals and outpatient costs, and more frequent resource-utilization, resulting in higher health-economic burden for the statutory healthcare system.

1. Introduction

Phenylketonuria (PKU) is an inherited metabolic disorder characterized by a deficiency in the enzyme phenylalanine hydroxylase (PAH), which results in elevated levels of phenylalanine (Phe) and reduced levels of tyrosine [1]. PKU is caused by over 1,000 different gene variants of PAH [2] and the severity of the resulting disease ranges from mild to severe based on the level of Phe in the blood and tissues [1,3]. Poorly managed PKU in childhood can result in a variety of symptoms including intellectual disability, seizures, behavioral problems, and mental disorders [4].

Management of PKU should start within the first 10 days of life (requiring timely diagnosis via newborn screening programs) to prevent irreversible damage (e.g. neurological impairment and mental retardation) and should be maintained throughout life to control neuropsychological and neurocognitive symptoms (e.g. slow reaction times and impaired inhibition, attention, and working memory) [5]. Strict control of blood Phe levels is of primary importance for optimal outcomes, particularly during the first years of life [5,6]. The dietary management of PKU comprises the reduction of dietary intake of Phe from natural sources, Phe-free amino acid supplements, and/or low-protein supplements/foods. Additionally, sapropterin dihydrochloride (a synthetic version of tetrahydrobiopterin [BH_4], the natural co-factor of PAH) can be used in responsive patients to increase residual PAH activity [7,8]. Dietary management options are ineffective in many adults with PKU due to long-term adherence issues [9–11] or inadequate Phe-lowering effects [7]. Moreover, a long-term PKU diet is associated with vitamin and/or mineral deficiencies [12–14] and an increased risk of low bone density [5]. Also, it is reported that women with PKU appear particularly vulnerable to excess weight gain and are more often obese

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than men with PKU [15]. Nevertheless, treatment for life is recommended for any patient with PKU, even though dietary management is associated with a significant patient burden [5].

The impact of this disease on individual patients and the healthcare system can only be understood when considering all involved healthcare domains and healthcare resources utilized by patients with PKU. As PKU is often associated with neurological, neuropsychiatric, behavioral, and cognitive symptoms, as well as a variety of somatic comorbidities [16], these conditions can also have a major impact on the health economic burden of patients with PKU.

The aim of this study was to assess the healthcare resource utilization and the associated costs of adult patients with PKU in Germany to gain insights into the health economic burden of adult patients with PKU.

2. Methods

2.1. Study design

This study was designed as a retrospective, matched-cohort analysis comparing adult patients with PKU (ICD-10 E70.0) and controls without PKU. The study utilized German statutory health insurance (SHI) claims data.

2.2. Data source

The Institut für angewandte Gesundheitsforschung Berlin (InGef) database contains anonymized healthcare claims of approximately 4,000,000 individuals. It is adjusted to the overall German population in terms of age and gender and is considered to be in good accordance to the overall German population for measures of morbidity, mortality, and drug usage [17]. The InGef database includes a geographically well-distributed population from all federal states of Germany. Approximately 70 (out of 120) different insurance companies contribute to the database, which includes verified claims data as originally used for reimbursement purposes. These claims data were used in this study in accordance with German Social Law. Data on patients and physicians is anonymized, as are the providers and the health insurances, before data is made available to the InGef, ensuring compliance with the strict data protection regulations in Germany.

2.3. Study period

The study period was from January 1, 2010, to December 31, 2015. PKU patients were enrolled within this time frame (enrollment period) and the outcomes were analyzed for a 1-year period from January 1, 2015, to December 31, 2015 (observation period).

2.4. Study population

Adult PKU patients were identified by using International Statistical Classification of Diseases and Related Health Problems, 10th revision, German Modification (ICD-10-GM) codes (E70.0 [Classical phenylketonuria] or E70.1 [Other hyperphenylalaninemias]) in the inpatient (main or secondary discharge diagnoses) and/or outpatient setting (verified diagnoses) during the enrollment period. They were excluded if they were younger than 18 years of age on January 1, 2015, or if they were lost to follow-up due to a sickness fund switch within the outcomes observation period.

2.5. Subgroups

Adult PKU patients were divided into cohorts of early-diagnosed and late-diagnosed patients, based on their birth year in relation to the implementation of newborn screening for PKU in Germany between 1969 and 1970 [18]. Thus, adult PKU patients born prior to January 1, 1969 were defined as late-diagnosed.

2.6. Matching

For each adult PKU patient, ten controls were drawn from the InGef database via direct, exact matching, without replacement on age and sex. Non-PKU controls (no PKU diagnosis code in the enrollment period) were required to be continuously enrolled in the database during the enrollment and observation periods, except for patients who died in the observation period.

2.7. Outcomes

Total annual healthcare costs were analyzed in the observation period and also stratified by the different cost domains: inpatient care, outpatient care, pharmaceuticals (including dietary amino acid supplements), and devices and aids. Healthcare resource utilization was analyzed in terms of hospitalizations and length of stay of hospitalizations, as well as for outpatient visits by physician specialty.

All-cause mortality was analyzed in 2015 and was described as an annual rate. All-cause mortality was defined as any reason for death, as the database did not contain the cause of death.

Prevalence ratios (PR) were calculated for categorical variables and mean differences (MD) between study groups were calculated for continuous variables. Differences between the groups were tested using 95% confidence intervals (95% CI) of PR and MD values.

3. Results

3.1. Study population

Overall, 3,723,345 individuals in the InGef database were continuously enrolled during the study period from January 1, 2015, until December 31, 2015. Of these, 377 adult individuals with PKU were identified, resulting in a period prevalence of 10.13 per 100,000 individuals in 2015.

The majority of adult PKU patients was female (58.1%) and the mean age ± standard deviation (SD) of adult PKU patients in 2015 was 50.9 ± 20.4 years. Of the 377 patients in the adult PKU cohort, 161 (42.7%) patients were born after the implementation of newborn screening in 1969 (early-diagnosed) and 216 (57.3%) patients were born prior to the implementation of newborn screening (late-diagnosed). The mean age of early-diagnosed and late-diagnosed patients was 30.7 ± 8.2 years and 65.9 ± 12.1 years, respectively. There was a higher proportion of females in the early-diagnosed cohort (n = 101; 63%) than in the late-diagnosed cohort (n = 118; 55%) (Table 1).

Table 1
Age and gender of adult PKU patients.

	Adult PKU patients	Early-diagnosed adult PKU patients	Late-diagnosed adult PKU patients
N	377 (100%)	161 (42.7%)	215 (57.3%)
Age, years			
Mean (SD)	50.9 (20.4)	30.7 (8.2)	65.9 (12.1)
Median (range)	51 (18–96)	30 (18–46[a])	65 (46[a]–96)
Interquartile range (Q1–Q3)	33–67	24–37	56–76
Gender			
Female, *n* (%)	219 (58.1%)	101 (62.7%)	118 (54.6%)
Male, *n* (%)	158 (41.9%)	60 (37.3%)	98 (45.4%)

PKU, phenylketonuria; Q, quartile; SD, standard deviation.
[a] Both the maximum age of the early-diagnosed patients and the minimum age of the late-diagnosed patients was 46 years since age was determined on January 1, 2015, and dates of birthday are set to the first day of a quarter (January 1, April 1, July 1, October 1) in the database.

3.2. Mortality

The overall mortality of adult PKU patients in 2015 was 2.4% ($n = 9$) versus 1.3% ($n = 43$) in the matched controls. The difference between the two cohorts was not statistically significant (PR 1.9; 95% CI 0.93–3.79). All deceased patients were late-diagnosed PKU patients; no early-diagnosed PKU patients died in 2015.

3.3. Healthcare costs and resource utilization

Healthcare costs were analyzed as a total for 2015 and stratified by cost domains: inpatient care, outpatient care, pharmaceuticals including dietary amino acid supplements, and devices and aids.

3.4. Overall adult PKU population

Mean total healthcare costs per subject incurred in 2015 by adult PKU patients were 2.3 times higher than those of the matched controls: mean for PKU patients (mean$_{[PKU]}$) €5932; MD €3307, 95% CI €1736–€4879. Furthermore, mean costs for PKU patients were significantly higher for pharmaceutical costs (mean$_{[PKU]}$ €2533; MD €1912, 95% CI €1195–€2629) and outpatient costs (mean$_{[PKU]}$ €1063; MD €395, 95% CI €115–€675) (Fig. 1). Mean costs for inpatient resources (mean$_{[PKU]}$ €2054; MD €904, 95% CI -€293 to €2100) and for aids and remedies (mean$_{[PKU]}$ €282; MD €97, 95% CI -€10 to €203) also tended to be higher in the PKU cohort than in controls although the differences were not significant (Fig. 1). The greatest difference between the two cohorts was for pharmaceutical costs (including dietary amino acid supplements), which accounted for 57.8% of the MD in total costs. Although only 13.8% of the PKU patients were prescribed and filled a prescription for dietary amino acid supplements in 2015, 50.1% of the pharmaceutical costs were for dietary amino acid supplements (mean costs: €1268). Sapropterin dihydrochloride was prescribed for fewer than five PKU patients (<1.3%).

Overall, 22.8% of the adult PKU patients were hospitalized in 2015 compared with 17.3% of matched controls (PR 1.3; 95% CI 1.08–1.60). Hospitalized PKU patients had a longer mean length of stay compared with their matched controls (mean 16.9 versus 14.2 days; MD 2.7 days, 95% CI -0.63 to 5.89 days). Adult PKU patients had a mean of 0.5 hospital stays in 2015 (MD 0.2, 95% CI 0.05–0.31).

In total, the mean number of all-cause outpatient visits for adult PKU patients in 2015 was 24.6 versus 17.3 visits in the matched controls (MD 7.3, 95% CI 4.56–10.04). Looking at outpatient visits by physician specialty, those with statistically significant MD between adult PKU patients and controls were primary care physicians (mean$_{[PKU]}$ 8.5; MD 2.8, 95% CI 1.74–3.81), other physicians (e.g. dermatologists, anesthetists, ophthalmologists, etc.) (mean$_{[PKU]}$ 5.5; MD 1.3, 95% CI 0.53–2.07), and orthopedists (mean$_{[PKU]}$ 1.2; MD 0.3, 95% CI 0.03–0.66). See Table S1 for a complete list of outpatient visits by physician specialty.

3.5. Early-diagnosed adult PKU patients

Mean total healthcare costs per subject incurred by early-diagnosed adult PKU patients were 4.0 times higher compared with those of the matched controls (mean$_{[PKU]}$ €5443; MD €4070, 95% CI €2544–€5597). Costs for pharmaceutical therapy (mean$_{[PKU]}$ €3646; MD €3313, 95% CI €1987–€4639) accounted for the majority of this difference (81.4%). Fewer than five early-diagnosed PKU patients (<3.1%) received a prescription for sapropterin dihydrochloride and only 29.2% filled a prescription for dietary amino acid supplements (~70% were not receiving dietary amino acid supplements). Nevertheless, dietary amino acid supplements were responsible for 67.8% of pharmaceutical costs (mean dietary amino acid supplement costs: €2473). Compared with matched controls, mean costs for early-diagnosed PKU patients were also higher for inpatient costs (mean$_{[PKU]}$ €815; MD €295, 95% CI -€165 to €755), outpatient costs (mean$_{[PKU]}$ €752; MD €302, 95% CI €165–€438), and costs for aids and remedies (mean$_{[PKU]}$ €230; MD €160, 95% CI -€7 to €328) (Fig. 2).

Overall, 18.0% of the early-diagnosed adult PKU patients were hospitalized in 2015, compared with 10.4% of matched controls (PR 1.7; 95% CI 1.21–2.49). Hospitalized PKU patients had a shorter mean duration of stay compared with their matched controls (mean$_{[PKU]}$ 10.8 days; MD 4.7 days, 95% CI 1.33–8.01 days). However, early-diagnosed PKU patients had a mean of 0.3 hospital stays in 2015 compared to 0.2 among their matched controls (MD 0.1, 95% CI 0.02–0.27).

In total, early-diagnosed adult PKU patients had a mean of 18.5 all-cause outpatient visits in 2015, whereas the matched controls had a mean of 11.5 all-cause outpatient visits (MD 6.9, 95% CI 4.01–9.85). Looking at outpatient visits by physician specialty, those with statistically significant MD between early-diagnosed PKU patients and the controls were primary care physicians (mean$_{[PKU]}$ 5.1 visits; MD 1.6, 95% CI 0.70–2.59), gynecologists (mean$_{[PKU]}$ 2.8; MD 0.8, 95% CI 0.02–1.53), internists working as a primary care provider (mean$_{[PKU]}$ 2.1; MD 1.1, 95% CI 0.41–1.70), and pediatricians (mean$_{[PKU]}$ 0.7; MD 0.4, 95% CI 0.14–0.68). See Table S2 for a complete list of mean outpatient visits by physician specialty.

3.6. Late-diagnosed adult PKU patients

Mean total healthcare costs per subject incurred by late-diagnosed adult PKU patients were 1.8 times higher than those of the matched controls (mean$_{[PKU]}$ €6296; MD €2738, 95% CI €241–€5236). Inpatient costs (mean$_{[PKU]}$ €2977; MD €1358, 95% CI -€695 to €3441) accounted for the largest part of this difference (49.6%). Furthermore, mean

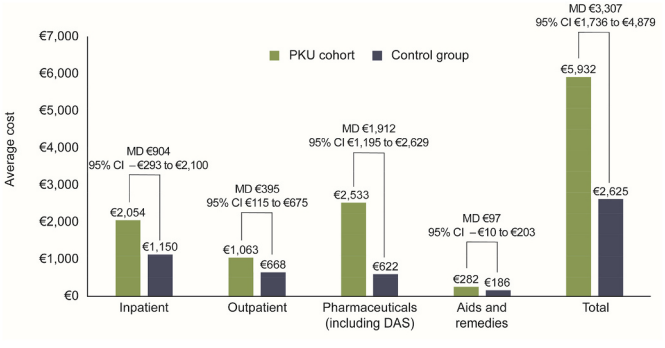

Fig. 1. Healthcare costs in total study population. Mean healthcare costs per subject in 1 year by category in adult patients with PKU and age- and gender-matched, non-PKU controls. CI, confidence interval; DAS, dietary amino acid supplements; MD, mean difference; PKU, phenylketonuria.

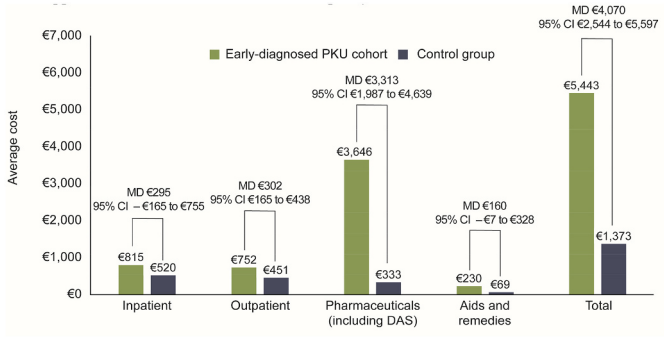

Fig. 2. Healthcare costs in early-diagnosed adult PKU patients. Mean healthcare costs per subject in 1 year by category in early-diagnosed adult PKU patients and age- and gender-matched, non-PKU controls. CI, confidence interval; DAS, dietary amino acid supplements; MD, mean difference; PKU, phenylketonuria.

pharmaceutical costs for late-diagnosed adult PKU patients were significantly higher than for their matched controls (mean$_{[PKU]}$ €1704; MD €867, 95% CI €116–€1618). Mean outpatient costs (mean$_{[PKU]}$ €1294; MD €829, 95% CI -€12 to €941) and costs for aids and remedies (mean$_{[PKU]}$ €322; MD €273, 95% CI -€88 to €186) also tended to be higher in late-diagnosed PKU patients compared with their matched controls, although the difference was not significant (Fig. 3). Only 2.3% of late-diagnosed adult PKU patients received dietary amino acid supplements, which accounted for 21.7% of the overall pharmaceutical costs (mean dietary amino acid supplement costs: €370). Moreover, none of the late-diagnosed PKU patients received a prescription for sapropterin dihydrochloride in 2015.

Overall, 26.4% of the late-diagnosed adult PKU patients were hospitalized in 2015, compared with 22.5% in matched controls (PR 1.2; 95% CI 0.92–1.48). Those PKU patients who were hospitalized had a longer mean duration of stay compared with their matched controls (mean 20.0 versus 13.8 days; MD 6.1 days, 95% CI 1.25–11.03 days). Late-diagnosed adult PKU patients had a mean of 0.6 hospital stays in 2015 compared to 0.4 in matched controls (MD 0.2, 95% CI 0.00–0.42).

In total, late-diagnosed adult PKU patients had a mean of 29.2 all-cause outpatient visits in 2015, compared with 21.6 among matched controls (MD 7.6, 95% CI 3.45–11.75). Looking at outpatient visits by physician specialty, those with statistically significant MD between late-diagnosed PKU patients and the controls were primary care physicians (mean$_{[PKU]}$ 11.1 visits; MD 3.6, 95% CI 2.04–5.20) and other physicians (e.g. dermatologists, anesthetists, ophthalmologists, etc.) (mean$_{[PKU]}$ 6.4; MD 1.1, 95% CI 0.14–2.15). See Table S3 for a complete list of mean outpatient visits by physician specialty.

4. Discussion

At present, there is very limited information on the health economic burden of adult PKU patients, in terms of costs and resource utilization, in Germany. This study demonstrates that PKU in adults is associated with a high health economic burden in Germany. Compared with age- and gender-matched controls without PKU, the PKU patients incurred 2.3 times higher annual healthcare costs. Pharmaceutical costs were the main cost driver in PKU patients and contributed 57.8% to the MD in total costs. More than half of the pharmaceutical costs were attributable to dietary amino acid supplements, even though the proportion of patients on dietary amino acid supplements was unexpectedly low (13.8%). Costs for inpatient care were shown to be the second cost driver in PKU patients, contributing 27.3% to the mean difference in total costs.

The high health economic burden was particularly evident in early-diagnosed PKU patients who had 4.0 times higher annual costs than their matched controls. Late-diagnosed PKU patients had 1.8 times higher annual costs than their matched controls. The burden was higher

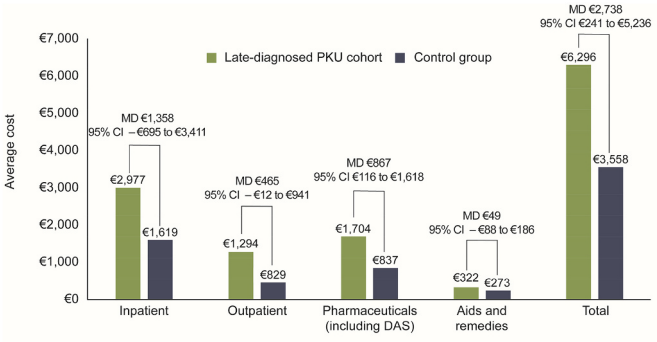

Fig. 3. Healthcare costs in late-diagnosed adult PKU patients. Mean healthcare costs per subject in 1 year by category in late-diagnosed adult PKU patients and age- and gender-matched, non-PKU controls. CI, confidence interval; DAS, dietary amino acid supplements; MD, mean difference; PKU, phenylketonuria.

for early-diagnosed PKU patients because of strongly increased costs for pharmaceuticals (MD €3313 for early-diagnosed PKU patients versus MD €867 for late-diagnosed PKU patients), even though late-diagnosed PKU patients incurred higher inpatient costs than early-diagnosed PKU patients when compared with matched controls (MD €295 for early-diagnosed PKU patients versus MD €1358 for late-diagnosed PKU patients). The higher inpatient costs for the late-diagnosed cohort are likely being driven up by their older age.

An exploratory study of the costs and reimbursement of special dietary foods used in the management of PKU in ten European specialist PKU centers confirms our findings that the most expensive items in the dietary management of PKU are dietary amino acid supplements [19]. As more than half of the pharmaceutical costs were attributable to dietary amino acid supplements, but only 13.8% of our study population received at least one prescription for dietary amino acid supplements, they can be defined as an important cost driver regarding the health economic burden of PKU. Other drugs that contributed to the pharmaceutical costs included those acting on the cardiovascular system, alimentary tract and metabolism, and nervous system. These drugs were prescribed significantly more often in PKU patients than in matched controls [16].

There are a few published studies that concentrate on the (cost-) effectiveness of newborn screening for metabolic diseases in Germany and in Europe [20,21]. A study from the United Kingdom (UK) using The Health Improvement Network database assessed the levels of healthcare resource use and corresponding costs over the first 36 years of life in PKU patients [22]. Comparisons of our findings to results of Guest et al. [22] are limited as this study assessed cumulative lifetime costs associated with PKU (versus annual costs in our study), and there are inherent differences in the healthcare system and reimbursement between Germany and the UK.

Further cost assessments on the burden of PKU in children, adolescents, and adults concentrated on the out-of-pocket costs for PKU patients, as well as for caregivers [23–26]. Most of the out-of-pocket costs were due to expenditures on low-protein food products [23]. The database used in this study did not contain out-of-pocket costs, but dietary amino acid supplements are reimbursable in German SHI. Besides out-of-pocket expenditures, PKU is associated with a high societal burden for caregivers in terms of invested time and financial loss due to lost earnings [24]. The utilized database in this study provides only very limited information on societal costs; therefore, we had to focus on the SHI perspective of the health economic burden of PKU.

A notable finding of this study was that 86.2% of adult PKU patients did not follow a dietary amino acid supplements diet, which could be reimbursed by the SHI, especially if they were late-diagnosed and, by definition, older (70.8% for early-diagnosed and 97.7% for late-diagnosed PKU patients). Even fewer patients were treated with sapropterin dihydrochloride (<1.3% of PKU patients). These findings are in line with results from Mlčoch et al. [27] who found that compliance with low-protein foods decreased with increasing age. This trend might indicate decreasing compliance as a strict diet imposes a burden on patients, but it could also be caused by decreasing management of older PKU patients due to former recommendations to not treat adult PKU [11,28]. Many adult PKU patients become lost to follow-up in their transition from pediatric to adult care [29] and many of these may be taken care of by general practitioners, who might be reluctant to prescribe dietary amino acid supplements because of lack of knowledge about PKU treatment and because of budget considerations (F. Rutsch, personal communication). Regarding the treatment of PKU patients with sapropterin dihydrochloride, it needs to be considered that sapropterin dihydrochloride is only effective in BH_4-responsive PKU patients [30], about 20–56% of PKU patients [31,32]. However, as we saw in the results, only <5 patients of our study population were treated with sapropterin dihydrochloride. This might suggest that other reasons besides the responsiveness to BH_4 are decisive factors for the treatment with sapropterin dihydrochloride. In a recent expert survey on the use of

sapropterin in PKU patients ≥16 years in Germany, only 11.8% of patients who were followed at a metabolic center were reported to be on sapropterin therapy [29]. In the current study, it is likely that a substantial proportion of patients was not continuously followed by a specialized center in Germany. General practitioners in Germany are more reluctant to prescribe sapropterin due to budget limitations (F. Rutsch, personal communication). Both of these factors may account for the low number of sapropterin prescriptions in the current study population.

In this study, more PKU patients required a hospital stay in 2015 compared with their matched non-PKU controls (22.8% versus 17.3%). Hospitalized PKU patients stayed an average 2.7 days longer in the hospital than the controls. Interestingly, early-diagnosed PKU patients had a higher chance of getting hospitalized in 2015 than late-diagnosed PKU patients compared with their matched controls (PR 1.7 in early-diagnosed versus PR 1.2 in late-diagnosed).

On average, PKU patients had 7.3 more outpatient visits in 2015. In early-diagnosed as well as in late-diagnosed PKU patients, a primary care physician was visited more often by PKU patients than their matched controls. Experience from a physician treating children with PKU confirms the suggestion that primary care physicians are crucial for the ongoing medical care of PKU patients besides the management in specific PKU centers [33]. On the other hand, a survey assessing the health-related quality of life of PKU patients in northern Germany found that frequency of annual physician visits in PKU patients does not significantly differ from the general population [34].

Early-diagnosed patients on average saw a pediatrician 0.7 times in 2015. As we only included PKU patients who are at least 18 years old, this is an interesting result. This indicates that the transition from pediatric care to adult care in Germany is lacking, due to a scarcity of adult specialists who treat PKU [35]. It is reasonable to assume that some patients might be followed up by their pediatrician since birth.

Moreover, early-diagnosed female PKU patients had visited a gynecologist more often compared with their matched controls. As 62.7% of the early-diagnosed PKU patients are female and are on average 30.7 years old, it is reasonable that early-diagnosed patients see a gynecologist more often than late-diagnosed PKU patients (on average 65.9 years old and 54.6% female). As maternal PKU is considered a high-risk pregnancy, the European PKU guidelines [5] recommend outpatient physician visits at least once during each trimester, but the intensity of monitoring should depend on individual needs and metabolic control, which is based on weekly Phe blood spots pre-conception and at least twice weekly during pregnancy. Maternal PKU is associated with two main risks for fetal development: growth retardation and birth defects including congenital heart defects. Therefore, a detailed follow-up by ultrasound examination is highly recommended from the very early beginning of pregnancy [5].

4.1. Strengths and limitations

In general, claims data analyses are subject to limitations, as they are primarily collected for reimbursement purposes and do not necessarily cover clinical parameters. Therefore, the study had to rely on the information that is coded in the utilized coding systems, namely the ICD-10-GM catalog. The ICD-10-GM catalog provides information about the disorders of aromatic amino-acid metabolism such as classical phenylketonuria (E70.0) and other hyperphenylalaninemias (E70.1) but contains no specific codes for severity of PKU. Therefore, we might see cases in the database with a very mild form of PKU, where no specific treatment or dietary management is necessary.

The stratification of the study population into early-diagnosed and late-diagnosed adult PKU patients was based exclusively on the year of birth in relation to the implementation of newborn screening for PKU, which was established in 1969/1970 in Germany. Individuals born prior to January 1, 1969 were classified as late-diagnosed PKU patients. This approach does not account for patients who were born in 1969/1970 who may or may not have undergone screening or patients who may have been born in other countries. It also does not account for newborns born prior to 1969 whose siblings already suffered from PKU and who therefore may have been tested and diagnosed early. Due to a disparity in the timing of the implementation of newborn screening between West Germany and the German Democratic Republic (GDR), the early-treated population from the united Germany may include some late-diagnosed patients originally from the GDR.

German claims data contains no direct information about the reason of death. Nevertheless, the data source provides sufficient information on overall mortality and the time of death.

Societal costs and patient individual costs were not considered in this study, as their assessment is strongly limited with claims data.

On the other hand, this study has some major strengths. First, the utilized data source allows the generalization of the results to the German SHI population. Second, participants of the German SHI system benefit from nearly full coverage of all healthcare services. Only small copayments exist in the German SHI. German claims data therefore provides a virtually comprehensive picture of all direct healthcare utilization. Furthermore, due to the large sample of approximately 4 million individuals in the InGef database, we identified a rather robust PKU patient sample size, which can sometimes be challenging concerning the rareness of the disease.

4.2. Generalizability

The InGef database is based on claims data from the SHI system, but is adjusted to the German overall population in terms of age and gender. The proportion of females in the SHI population is higher than in the overall German population because proportionately more males choose private health insurance in Germany. Moreover, the prevalence of PKU shows regional differences among the federal states in Germany. The adjusted age and sex distribution of the InGef database does not account for these regional differences [36].

5. Conclusions

This retrospective matched cohort analysis utilizing German SHI claims data demonstrated that PKU is associated with a high health economic burden in Germany. Costs for pharmaceuticals, especially dietary amino acid supplements, were revealed to be the cost driver, despite relatively few patients receiving dietary amino acid supplements and almost none receiving sapropterin dihydrochloride. Late-diagnosed (by definition, older) PKU patients were especially at risk of not receiving dietary amino acid supplements, indicating they are not being treated by a Phe-restricted diet as suggested by the European PKU treatment guidelines. Looking at early- and late-diagnosed PKU patients separately, most costs for late-diagnosed PKU patients were produced in the inpatient sector, whereas pharmaceuticals are the main cost driver in early-diagnosed PKU patients. PKU patients were hospitalized more often and stayed longer in the hospital compared with their matched controls. Also, in the outpatient sector, PKU patients utilized more healthcare resources regarding physician visits compared with their matched controls. Besides primary care physicians, gynecologists were visited significantly more often by early-diagnosed and therefore younger PKU patients. Overall, this study revealed the high health economic burden of PKU patients for the statutory healthcare system. Further research is needed to investigate the individual or societal economic burden of PKU.

Authors' contributions

KMS, JA, and CJ analyzed the dataset. All authors interpreted the data. KMS and PL were responsible for drafting an initial outline of the manuscript for review by all authors prior to development of a first draft. All authors provided critical review, revision of drafts, and approval of

the final manuscript.

Availability of data and materials

The utilized database in this study is available from the Intitut für angewandte Gesundheitsforschung Berlin (InGef) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data tables showing all included analyses are included in the supplementary materials.

Conflicts of interest

FT received honoraria for presentations from BioMarin. ACM has been a member of scientific advisory boards supported by BioMarin Europe Ltd. and has received honoraria as a speaker for BioMarin Europe Ltd. KMS, JA, CJ, and SB are full-time employees of Xcenda, acting as contractors of BioMarin Europe Ltd. for the execution of this study. AJ and MJ are employees and stockholders of BioMarin Europe Ltd. IA and PL were employees of BioMarin Europe Ltd. at the time of the study. CZ is an employee and stockholder of BioMarin Deutschland GmbH. FR has received speaker and consulting honoraria from BioMarin Europe Ltd. WG declares no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2021.100764.

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Modul 4

Healthcare costs and resource utilization of asthma in Germany: A claims data analysis

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ORIGINAL PAPER

Healthcare costs and resource utilization of asthma in Germany: a claims data analysis

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Abstract
Introduction Asthma is associated with a substantial economic burden on the German Statutory Health Insurance.
Aims and objectives To determine costs and resource utilization associated with asthma and to analyze the impact of disease severity on subgroups based on age and gender.
Methods A claims database analysis from the statutory health insurance perspective was conducted. Patients with an ICD-10-GM code of asthma were extracted from a 10 % sample of a large German sickness fund. Five controls for each asthma patient matched by age and gender were randomly selected from the same database. Costs and resource utilization were calculated for each individual in the asthma and control group. Incremental asthma-related costs were calculated as the mean cost difference. Based on prescribed asthma medication, patients were classified as intermittent or persistent. In addition, age groups of ≤5, 6–18, and >18 years were analyzed separately and gender differences were investigated.
Results Overall, 49,668 individuals were included in the asthma group. On average, total annual costs per patient were €753 higher ($p = 0.000$) compared to the control group (€2,168 vs. €1,415). Asthma patients had significantly higher ($p = 0.000$) outpatient (€217), inpatient (€176), and pharmacy costs (€259). Incremental asthma-related total costs were higher for patients with persistent asthma compared to patients with intermittent asthma (€1,091 vs. €408). Women aged >18 years with persistent asthma had the highest difference in costs compared to their controls (€1,207; $p < 0.0001$). Corresponding healthcare resource utilization was significantly higher in the asthma group ($p = 0.000$).
Conclusions The treatment of asthma is associated with an increased level of healthcare resource utilization and significantly higher healthcare costs. Asthma imposes a substantial economic burden on sickness funds.

Keywords Asthma · Claims data · Cost of illness · Disease severity · Persistent · Intermittent

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Introduction

Asthma is a chronic inflammatory disorder of the airways and one of the most common chronic diseases in Germany. About 10 % of the pediatric population is suffering from asthma [1–4] followed by adults with about 5 % [5–8]. The prevalence of asthma in the Statutory Health Insurance (SHI) is approximately 6 % [2]. Depending on the severity of the disease, asthma poses a considerable burden on

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affected individuals, resulting in loss of productivity and participation in family life [9]. The disease also represents a constant major economic burden for the German statutory healthcare system [2, 10, 11] with approximately €1.789 billion in 2008, accounting for 0.7 % of the total healthcare expenditure in Germany [12]. Several studies have assessed the costs of asthma in the German setting, considering a payer's perspective or a societal perspective [2, 5, 10, 11, 13–16]. Yet, further research is required as data of the available studies is fragmentary and does not include all relevant cost domains. Due to methodological limitations, the reported results for the resource use and costs strongly rely on assumptions, which are associated with uncertainty. Moreover, most studies used cost data that can be considered as obsolete reaching from 1992 to 2000 as reference years for cost calculation. Former studies reported disease severity as a considerable factor, with a significant impact on total asthma costs [11, 17]. Hence, a detailed analysis of the influence of disease severity on resource use and costs is advisable. The aim of this study was to identify resource utilization for patients with asthma and the average disease related costs on an individual patient level. Further objectives were to analyze the impact of disease severity for subgroups based on age and gender, which is still lacking for the German setting [18].

Materials and methods

Data and study population

Claims data from German sickness funds include age and gender of the insured individual and detailed reimbursement-related data for outpatient care, inpatient care, pharmaceuticals, therapeutic devices, rehabilitation, and sick leave. Every single healthcare service reimbursed by the sickness fund can be identified and analyzed. All information on the different healthcare services can be linked on an individual patient level via a unique identification code. [19].

Anonymized claims data from the largest German sickness fund (Techniker Krankenkasse) were analyzed. The sickness fund covered approximately 8 million persons in 2010. Patients with a diagnosis code of asthma (International Statistical Classification of Diseases and Related Health Problems, 10. Revision, German Modification ICD-10-GM; Asthma bronchiale: J45.0, J45.1, J45.8, J45.9; Status asthmaticus: J46) were identified in the inpatient or outpatient setting. Primary and secondary diagnosis codes in the inpatient setting and confirmed diagnosis codes in the outpatient setting were taken into account. The criterion "confirmed" is an additional attribute in the outpatient data. It clarifies the certainty of the diagnosis. The study period was from January 1, 2010 to December 31, 2010. Patients were required to be continuously insured within the study period. Individuals who died in the study period were excluded from the analysis. Due to data protection regulations, a 10 % random sample of all identified asthma patients was used for further analyses.

To reflect disease severity, all asthma patients were stratified as having either intermittent or persistent asthma. The classification was based on prescribed asthma medication. Patients with a record of any of certain asthma medications (long-acting β_2-agonist (LABA; ATC: R03AC13, R03AK07, R03AK72, R03AC12, R03AK61, R03AK06, R03CC12, R03CC13, R03CC14, R03CC63, R03AK71), leukotriene modifiers (LTRA, ATC: R03DC03), inhaled corticosteroid (ICS; ATC: R01AD01, R03BA01, R03BA02, R03BA08, R03BA05, R03BA07), oral corticosteroid (OCS; ATC: H02AB03, H02AB04, H02AB07, H02AB06, H02AB56, H02AB08), Anti-IgE; ATC: R03DX05), Theophylline (ATC: R03DA04, R03DA54), and ipratropium bromide (ATC: R03BB01) or a documented hospitalization with a primary diagnosis of asthma (ICD-10-GM; Asthma bronchiale: J45.0, J45.1, J45.8, J45.9; Status asthmaticus: J46) were classified as having persistent asthma; whereas patients receiving only reliever medication (i.e. at least one prescription of a short-acting β2-agonist; ATC: R03AC04, R03AK03, R03AK05, R03AC02, R03CC02, R03AC03, R03CC03) or no asthma specific medication were classified as having intermittent asthma.

In addition to the observation of the whole study population, different age groups of ≤5, 6–18, and >18 years were analyzed. Moreover, differences in gender groups were investigated.

Control group design

A randomly selected control group of individuals without asthma was extracted from the population of the participating sickness fund. To ensure the control group had no history of asthma, these insured persons were required to have an asthma diagnosis-free record for the time of the study period and the 2 years prior to that time frame. Five controls were matched exactly by year of birth and gender to each selected asthma patient.

Calculation of costs and healthcare resource utilization

Costs and healthcare resource utilization (HRU) were calculated from the perspective of the statutory health insurance. Patient co-payments or out-of-pocket payments were not considered. German healthcare insurance covers almost all accruing costs [20]. All costs were calculated on an annual scale for each individual patient in the asthma and in the control group. Costs were calculated separately for each of the six domains—outpatient care, inpatient care,

pharmaceuticals, therapeutic devices and remedies, rehabilitation, and sick leave payments to identify potential cost drivers. Outpatient care covers all costs for services performed in an outpatient setting. Inpatient care summarizes all costs of performed services and administered drugs during inpatient stays. Pharmaceuticals include the costs of drug prescriptions in the outpatient setting. Therapeutic devices (Hilfsmittel) are devices such as walkers and wheelchairs to support the patient in recovering and everyday care. Remedies (Heilmittel) are services such as massages or occupational therapy provided by medically trained personal. The costs of rehabilitation are covered by the sickness fund for individuals who are not part of the workforce such as children and retirees. The costs of sick leave payments are covered by the sickness funds for employees beginning with the seventh week of sick leave, the first 6 weeks have to be paid by the employer. Total costs were calculated as the sum of the six domains. Asthma-related costs were calculated as the mean cost difference between the costs of the asthma group and the matched control group (incremental approach).

The reimbursement of services in the outpatient care setting in Germany is regulated by the Uniform Valuation Scheme (EBM). The majority of services are not invoiced directly by means of a monetary value but by a system of weighted points. Euro-based charges can be accounted for selected services, such as transportation, documentation, and some screening. To assess the monetary payment in the outpatient setting, the weighted points are usually multiplied by a uniform orientation value, which is defined by the National Association of Statutory Health Insurance Physicians [21]. Weighted points for the year 2010 were multiplied by a uniform orientation value of 0.035048 euros [22].

The utilization of healthcare resources was assessed in terms of the numbers of outpatient visits, number of inpatient visits, number of days in the hospital, number of prescriptions, number of therapeutic devices and remedies, number of days of sick leave payment for the sickness fund, and number of days of rehabilitation. Outpatient visits were approximated by counted dates of invoiced EBM codes. In line with the cost calculation, the asthma-related resource utilization was calculated as the mean difference in each category between the asthma group and the control group (increment).

Statistical testing was applied by using a *t* test to determine the significance of differences in healthcare resource utilization and costs.

Results

A total of 49,668 individuals with ICD-10-GM asthma coding in 2010 are included in the study, as well as 248,340 individuals for the control group approach. The study population consists of 51.5 % females and 48.5 % males; the average age in both groups is 38.5 years.

On average, patients with asthma have more outpatient and inpatient visits, a higher amount of prescriptions for pharmaceuticals and likewise for therapeutic devices and remedies, more days in hospital, more days of sick leave payments, and more days of rehabilitation in 2010 in contrast to the control group (see Table 1). The number of outpatient visits and the number of prescriptions are significant with approximately six more consultations per year and almost twice as many drug prescriptions as compared to their controls.

The calculation of mean annual costs per patient for the asthma group results in total costs of €2,168 in 2010. Most of these costs are attributable to inpatient care (29.8 %), outpatient care (28.9 %), and pharmacotherapy (25.8 %). Therapeutic devices and remedies (7.4 %) and sick leave payments (6.4 %) are also relevant but less important. Rehabilitation costs only account for 1.6 % of the total costs (see Table 2).

In contrast, mean annual costs for an insured person in the control group totaled €1,415. Inpatient care was also the cost driver (33.2 %). The share of outpatient care (28.9 %) was equal compared to the asthma group whereas the share of pharmacotherapy (21.3 %) was slightly lower. The costs for therapeutic devices and remedies (8.7 %) and for sick leave payments (6.5 %) also played a minor role. The impact of rehabilitation costs (1.5 %) on the total costs was negligible.

The control group design enables the calculation of disease-related costs for asthma by subtracting the mean costs per domain of the asthma group from the mean cost per domain of the control group. In contrast to the overall costs per asthma patient, incremental asthma-related costs (see Table 2) are highest for pharmacotherapy with €259 (34.4 %). Outpatient care (29.0 %) and inpatient care (23.4 %) are still major components of the asthma-related total costs. Sick leave payments (6.2 %) and therapeutic devices and remedies (5.1 %) have a slightly smaller share than in the overall cost perspective. Rehabilitation remains of minor importance.

Several studies have suggested that asthma-related costs increase with disease severity [11, 13]. To investigate the impact of disease severity on cost levels, patients were grouped into individuals with intermittent and persistent asthma. According to our classification algorithm, 52 % of the asthma patients have persistent asthma. An additional stratification of patients by gender and age groups provides even more detailed information of the distribution of disease-related costs (see Table 3). Annual total costs and incremental asthma-related costs are higher for patients that were classified as having persistent asthma. For both

Table 1 Mean healthcare resource utilization in 2010

Type of resource utilization	Asthma group ($n = 49{,}668$)	Control group ($n = 248{,}340$)	Incremental asthma-related healthcare resource utilization (difference of means)
Number of all outpatient visits	16.47	10.74	5.73***
Number of all hospitalizations	0.25	0.17	0.08***
Number of days in hospital	1.79	1.23	0.56***
Number of drug prescriptions	11.22	5.79	5.43***
Number of therapeutic devices and remedies	1.13	0.74	0.39***
Days of sick leave payment	2.49	1.61	0.88***
Days of rehabilitation	0.29	0.21	0.08***

Significant $\alpha = 0.05$;
*** p value $= 0.000$

Table 2 Costs of asthma patients and incremental asthma-related costs in 2010 in euros

Type of cost	Asthma group[a]				Control group[b]	Incremental asthma related
	Minimum	Maximum	Standard deviation	Mean	Mean	Difference of means
Outpatient care	0	34,019	904	627	409	218***
Inpatient care	0	161,855	3,044	645	469	176***
Pharmaceuticals	0	390,423	3,213	560	301	259***
Therapeutic devices and remedies	−257[c]	41,667	674	161	123	38***
Rehabilitation	0	29,321	436	36	21	15***
Sick leave payments[d]	0	55,132	1,647	139	92	47***
Total	−3[c]	399,180	5,740	2,168	1,415	753***

[a] $n = 49{,}668$, [b] $n = 248{,}340$, significant $\alpha = 0.05$; *** p value $= 0.000$

[c] Claims data is collected for accounting purposes. Negative costs might occur as a result of reversals and regresses

[d] A total of 1,087 individuals in the asthma group (2.2 %) and 3,831 individuals in the control group (1.5 %) received sick leave payments

genders, asthma-related costs are highest in the age group over 18 years with persistent asthma.

Discussion

Considering the widespread prevalence of asthma in the German population, the economic burden of the disease is a significant challenge for the Statutory Health Insurance. Pharmacotherapy and outpatient care are the major cost drivers for incremental asthma-related costs, which is consistent with existing literature [2, 13]. The costs for inpatient care are still considerable with 23 % of the asthma-related costs.

Depending on patient characteristics and asthma severity, overall and incremental asthma-related costs might vary substantially. On average, overall total costs per patient with asthma were lowest with €723 in the group of females from 0 to 5 years with intermittent asthma or wheezing. In contrast, the lowest mean cost for the treatment of asthma is €107 within the group of females from 6 to 18 years. The highest mean overall incremental asthma-related costs were found in the group of women with persistent asthma above the age of 18 and amounted to €1,208.

Although randomly selected, the proportion of male and female patients in the study sample reflects the data on 12-month asthma prevalence presented in the literature. In the childhood population, the 12-month asthma prevalence of male patients is higher (3.4–11.8 %) compared to female patients (2.5–9.2 %) [1–3], whereas in the adult population, women are more likely to have asthma with a 12-month prevalence of 6.2 % compared to adult men with 4.2 % [7].

The strength of the present study is its potential to describe the resource utilization and costs of asthma under real-life conditions and for the whole spectrum of services reimbursed by the Statutory Health Insurance system. Moreover, we are able to show that asthma is more expensive compared to the age- and gender-matched sickness fund population. Due to the nature of German sickness fund claims data, the presented resource utilizations and costs provide a complete picture of all health services reimbursed by the sickness fund on the patient level. This is one of the key advantages of this data source for the execution of health economic analysis from the perspective

Table 3 Annual incremental asthma-related costs for patients with intermittent and persistent asthma in euros

Age group	Study group	Intermittent asthma						Persistent asthma					
		Female patients			Male patients			Female patients			Male patients		
		N	Mean (SD)	Incremental asthma related	*N*	Mean (SD)	Incremental asthma related	*N*	Mean (SD)	Incremental asthma related	*N*	Mean (SD)	Incremental asthma related
0–5 years[1]	Asthma	268	723 (1,121)	140	368	932 (2,253)	213	401	1,521 (3,431)	861***	614	1,499 (2,636)	778***
	Control	1,340	583 (1,386)		1,840	719 (1,554)		2,005	660 (2,444)		3,070	721 (2,250)	
6–18 years	Asthma	1,890	782 (1,348)	107	2,815	1,015 (8,010)	359*	1,669	1,504 (3,308)	909***	2,685	1,335 (2,857)	678***
	Control	9,450	675 (2,678)		14,075	656 (3,412)		8,345	595 (2,249)		13,425	657 (3,355)	
Over 18 years	Asthma	9,958	2,021 (5,842)	528***	8,457	1,783 (5,635)	369***	11,366	2,937 (5,456)	1,208***	9,177	2,899 (6,846)	1,133***
	Control	49,790	1,493 (4,158)		42,285	1,414 (5,525)		56,830	1,729 (4,690)		45,885	1,766 (5,993)	

Significant $\alpha = 0.05$; * p value <0.01; *** p value = 0.000

[a] These patients might also be classified as wheezers. According to GINA [9] asthma-related symptoms like wheezing commonly occur in children aged 5 years and younger without asthma. Therefore, it is difficult to classify these patients as having asthma

of the sickness fund compared to other primary and secondary data sources [19].

This is the first study for Germany that consistently reports the cost of illness for asthma from the perspective of the SHI using claims data. Stock et al. [2] calculated direct costs of €48.2 million for asthma-related hospitalization, €62.5 million for inpatient rehabilitation, and €579.7 million for asthma-specific medication using claims data and data from national statistics for the year 1999.

Schramm et al. [13] reported direct costs for patients with asthma and seasonal allergic rhinitis in a range from €569 per adult patient with only seasonal allergic rhinitis to €2,048 for patients with severe asthma and seasonal allergic rhinitis for the year 2000. Data for cost calculation was collected by patient questionnaires and patients' records. The study population consisted of 500 individuals.

Weinmann et al. [14] investigated the costs of asthma in children resulting in average treatment costs of $627 per year. Data was collected from chart review of the involved physicians. Costs were calculated on a 1996 basis and converted to US$. A total of 76 children with asthma participated in the study.

Weißflog et al. [10] estimated total asthma costs of €2.97 billion for the German setting in 1996 using data from the AOK sickness fund statistics and the statistical yearbook. Direct asthma costs were €1.92 billion.

Schulenburg et al. [11] analyzed data from 216 asthma patients in Germany collected by questionnaires in participating doctor's offices. Direct asthma costs of adult patients ranged from €1,060 to €4,073 with increasing disease severity. The direct asthma costs for children increased from €1,327 to €2,460, respectively. The calculation was based on 1994/95 cost information.

Nowak et al. [5] estimated the costs of asthma for Germany. Direct asthma costs amounted to €1.613 billion in 1992. Data was collected from available literature sources and extrapolated to the German population.

A recent review from Kirsch et al. [16] estimated annual asthma-specific costs of €445 to €2,543 per patient from the social perspective. Cost data was collected from published cost-of-illness studies and adjusted for the year 2010. Direct asthma costs ranged from €175 to €1,718 and were reported in detail for outpatient care (€109–€292), inpatient care (€12–€100), pharmaceuticals (€139–€484), and rehabilitation (€9–€64). Sick-leave payments (€64–€379) were also reported, but were not part of the calculation of total asthma costs. The reported cost data provides an estimate of the costs of asthma from a social and the payer's perspective using the available data.

Nevertheless, none of the included studies considered all relevant cost domains and the calculations were mostly based on assumptions or were estimated when specific data were missing or were not detailed enough. The present

cost-of-illness study fills the gap by considering all relevant cost domains from the perspective of the sickness fund. Because sickness fund claims data contain all reimbursed services attached to single individuals, the results in this study are more precise than the former assumption-based calculations. Moreover, our study provides deeper insights into the distribution of asthma costs and related resource utilizations for different age groups, gender, and disease severity.

The study design with a control group approach is a valid instrument to calculate asthma costs based on the difference in total healthcare costs (incremental costs). These incremental asthma-related costs not only cover direct treatment costs of asthma but also the costs of an increase of co-morbidities and a worsening of already existing co-morbidities. The large asthma group and the even bigger control group with five controls per asthma patient ensure a robust calculation of incremental asthma-related costs [19].

Besides the strengths of the present study, there are some limitations that should be presented. There is only limited socio-economic information available in the claims data of German sickness funds. Information regarding age and gender of the insurant is available, but no further information concerning social status or income. Moreover, information about quality of life and behavior patterns like smoking are not covered in the data [23]. Therefore, a matching of investigated individuals with their controls is only possible by age and gender. Other patient characteristics that might influence resource utilization and reimbursement could not be considered by this approach.

Another limitation associated with claims data analysis in general and with the present study in particular is the absence of clinical information (e.g., results of laboratory test or blood pressure, in this case lung function, allergic status) [24]. Therefore, it is not possible to definitively distinguish between different asthma control stages or severities. As a proxy, we used the claims for asthma-related medication to approximate the disease severity for each patient.

Inpatient stays in Germany are reimbursed via a diagnosis-related group (DRG)-based system where a fixed amount is paid depending on the DRG per case. The amount differs with some parameters (e.g., the presence of complication), but not with the medication administered during the stay. All medication is reimbursed by the fixed amount per DRG. Therefore, no separate documentation exists within the claims data of a German sickness fund for the administered medication within an inpatient stay [25]. In fact, the applied algorithm to classify asthma severity relies on information of the prescribed medication. Patients with no record of an asthma-specific medication but with an asthma-related inpatient stay were classified as having persistent asthma if the asthma diagnosis was recorded as the primary diagnosis and as having intermittent asthma if the asthma diagnosis was recorded as the secondary diagnosis. There might be cases where this approach leads to a misclassification of the very patient. However, there were only 192 cases where that rule was applied. From a clinical standpoint, these individuals should be classified as patients with persistent asthma.

In practice, health care services in the outpatient setting are reimbursed by a fixed amount paid by the sickness funds to the Associations of Statutory Health Insurance Physicians (KV) on a quarterly basis. This practice limits the costs for outpatient services from the perspective of the statutory health insurance. Nevertheless, Braun et al. [26] recommended a monetary attribution of weighted points of the Uniform Valuation Scheme (EBM)—as adopted in this study—to take opportunity costs into account. Opportunity costs might occur because of more time-consuming services for specific diseases as physicians have only limited timely resources to treat all their patients. However, monetary values for weighted points differ in the accounting practices in the particular administrative districts of the National Associations of Statutory Health Insurance Physicians. Therefore, an average value was used to assess the invoiced Uniform Value Scale points and transform them into a monetary value. Differences from that mean value might occur in some regions and therefore under- or overestimate the monetary value of an invoiced service for a specific region.

Some services in the outpatient setting are only reimbursed once per quarter. Therefore, the calculation of outpatient visits by counting the dates of invoiced EBM codes per patient might result in an underestimation of actual number of outpatient visits. However, these uncounted outpatient visits result in no additional costs from the payer perspective.

Finally, by using only data of the biggest German sickness fund, although nationwide, the results might not be fully representative for the whole German Statutory Health Insurance population.

Conclusions

Considering the widespread prevalence of the disease in the German population, the economic burden is significant. Incremental asthma-related costs vary substantially according to disease severity and patient characteristics. They increase considerably with higher age and the manifestation of persistent asthma. As for the resource use, the disease results in a significantly higher utilization of healthcare resources, not only drugs but also outpatient care as well as inpatient care. To direct future

interventions, like disease management programs, further research regarding the diversity of asthma characteristics and especially the identification of high-cost patient groups is needed.

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Modul 5

Assessing asthma severity based on claims data: A systematic review

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ORIGINAL PAPER

Assessing asthma severity based on claims data: a systematic review

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Abstract
Introduction Asthma is one of the most common chronic diseases in Germany. Substantial economic evaluation of asthma cost requires knowledge of asthma severity, which is in general not part of claims data. Algorithms need to be defined to use this data source.
Aims and objectives The aim of this study was to systematically review the international literature to identify algorithms for the stratification of asthma patients according to disease severity based on available information in claims data.
Methods A systematic literature review was conducted in September 2015 using the DIMDI SmartSearch, a meta search engine including several databases with a national and international scope, e.g. BIOSIS, MEDLINE, and EMBASE. Claims data based studies that categorize asthma patients according to their disease severity were identified.
Results The systematic research yielded 54 publications assessing asthma severity based on claims data. Thirty-nine studies used a standardized algorithm such as HEDIS, Leidy, the GINA based approach or CACQ. Sixteen publications applied a variety of different criteria for the severity categorisation such as asthma diagnoses, asthma-related drug prescriptions, emergency department visits, and hospitalisations.
Conclusion There is no best practice method for the categorisation of asthma severity with claims data. Rather, a combination of algorithms seems to be a pragmatic approach. A transfer to the German context is not entirely possible without considering particular conditions associated with German claims data.

Keywords Asthma · Claims data · Exacerbation · Persistent · Intermittent · Systematic review · HEDIS · Leidy · GINA · Economic evaluation

Introduction

Asthma is one of the most common chronic diseases, diagnosed in about 10 % of children and 4–5 % of the adult population in Germany [1]. The economic burden for the German Statutory Health insurance has increased gradually from 2002 to 2008 up to €1,789,000,000 for the year 2008 [2]. The treatment of asthma varies based on the severity of symptoms and disease manifestation. An insufficiently treated asthma patient can suffer from life-threatening asthma attacks with the need for emergency hospitalisation. It is generally accepted that both asthma burden, i.e. for patients in terms of quality of life etc., and treatment costs increase with asthma severity and insufficient control [3]. Substantial economic evaluation of asthma costs requires knowledge of asthma severity, which is generally assessed by using clinical information from the patient. Asthma is a heterogeneous disease whose symptoms can vary over time, and that can change rapidly from day to day. Given that the disease is well-characterized in some patients, the relationship between the underlying disease processes and their

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clinical manifestations may not be strong. This issue poses a challenge regarding how patients with asthma should be diagnosed and assessed, and how treatment should be adjusted [4]. The concept of asthma severity itself has evolved substantially over the years. Previous Global Initiative for Asthma (GINA) guidelines have differentiated asthma severity into four categories: intermittent, mild persistent, moderate persistent, and severe persistent, referring to the clinical characteristics before treatment and the magnitude of disease features such as the severity of airway obstruction [5]. A patient's treatment is decided based on this severity classification. As the clinical perspective of asthma has been refined over the years, now focussing more on asthma control rather than on severity, the assessment of severity from a health economic perspective is still of importance given the possibilities of disease management [3]. In general, severity reflects the underlying disease manifestations and thus helps targeted treatments. Furthermore, maintaining a concept of asthma severity includes the option of referring to patients with whom asthma management is challenging either due to poor adherence or, although being adherent, requiring high-intensity treatment [4]. These patients absorb a high proportion of asthma health resources, which is relevant from a health economic perspective.

Hence, not only is the level of asthma control important in terms of the treatment required to achieve adequate asthma treatment, but also the corresponding asthma severity.

Claims data offer important advantages for economic evaluations by providing observational information for a large number of patients, which reflect decisions made both by health care providers in routine clinical practice and by patients with regard to prescription fills and use of inpatient and outpatient care [6]. German claims data include information on an individual patient level such as: biographic data (e.g. age, gender, etc.), healthcare resource utilisation and direct healthcare costs for outpatient and inpatient procedures, drugs, devices and aids, occupational therapies, sick leave payments (with reason) and early retirement. German healthcare insurances cover the most health care services, resulting in only marginal patient co-payments. Healthcare provider payments on the expense of sickness funds (hospital, physician, or pharmacist) represent almost the complete direct health care costs on an individual basis. Due to federal data protection laws, claims data do not include direct clinical data input, such as measures of lung function, forced expiratory volume (FEV) or peak expiratory flow (PEF). Considering that no direct clinical data is captured in claims data, methods to identify different disease severities and disease worsening are needed in order to be able to use this data source for economic evaluation [7]. A variety of algorithms has been developed over the past two decades to fill this gap. Healthcare Effectiveness Data and Information Set (HEDIS) is a quality measurement program from the National Committee for Quality Assurance developed on a claims data based definition of persistent asthma. This definition relies on asthma-coded medical visits and asthma-related pharmacy claims. According to this definition, a population can be identified for whom asthma controller therapy is indicated [8]. In order to be identified as a persistent asthma patient, one or more of the following criteria must be met for the current year: at least one emergency department (ED) visit with asthma as the principal diagnosis, or at least one acute inpatient claim/encounter with asthma as the principal diagnosis, or at least four outpatient asthma visits with asthma as one of the listed diagnoses and at least two asthma medication dispensing events, or at least four asthma medication dispensing events [6, 9, 10]. Recent publications have modified the HEDIS criteria to a 2-year timeframe for the assessment of the above described criteria [11–17]. Although the HEDIS criteria was first used for claims data studies by Berger et al. [18], a validation of the criteria was lacking until 2010. Schatz et al. [8] used survey data including medication use, asthma symptoms and the presence of exacerbations to validate the HEDIS criteria.

The Leidy method [19] determines mild persistent asthma based on the frequency of claims for β_2-agonist combined with the frequency of claims for oral corticosteroid prescriptions (OCS). Mild persistent asthma is defined by four to six short-acting β_2-agonist (SABA) refills and zero oral OCS prescriptions per year, or two to three SABA refills and less than two OCS prescriptions per year. Furthermore, one (or less) SABA refill and one oral OCS prescription per year can also account for mild persistent asthma. Moderate persistent asthma includes more than six SABA refills and less than two OCS prescriptions per year, or four to six SABA refills and one to two OCS prescriptions per year. Patients with severe persistent asthma are required to have more than six SABA refills per year and the number of OCS prescriptions per year is greater than or equal to two. Moreover, zero to six SABA refills and three or more SABA prescriptions per year also constitute severe persistent asthma. Clinical validation of the Leidy criteria is warranted [19].

The current GINA guideline provides recommendations for categorizing levels of asthma control. However, previous GINA documents have subdivided asthma by severity based on the level of symptoms, airflow limitation, and lung function variability. Four categories were included: intermittent, mild persistent, moderate persistent, and severe persistent [20]. The daily dose of inhaled corticosteroids (ICS) and long-acting β_2-agonist LABA were divided into low and high intensity treatment. Mild

persistent asthma was defined by either using low-dose ICS consistently, or using ICS inconsistently, including zero to two claims. Patients with moderate persistent asthma were defined as such if they received low-dose ICSs and either a LABA, a leukotriene modifier, theophylline or medium- or high-dose ICSs. Severe persistent asthma was defined by the use of medium- or high-dose ICS plus a LABA along with other controllers [20]. A validation of the GINA based claims data algorithms is still lacking.

The Canadian Asthma Consensus Guideline (CACQ)-based database indexes were developed and validated by Firoozi et al. [21]. The severity index defines three levels of asthma severity by assessing asthma medication and the presence of moderate/severe asthma exacerbations over a period of 1 year. Patients in the mild asthma category are supposed to show no presence of moderate/severe asthma exacerbations over a period of 1 year, receive ICS doses of 0–500 μg/day with no additional controller therapy or, for patients with additional controller therapy, a dosage of 0–250 μg ICS per day. Moderate asthma is classified by ICS doses of >500 μg/day for patients without additional controller therapy, and doses of >250 μg/day for those with additional controller therapy. Patients with high use of SABA and moderate or severe asthma exacerbations are also classified as moderate asthma. The category of severe asthma consists of individuals receiving ICS doses of >1000 μg/day, or >10 doses of SABA per week, with moderate/severe exacerbations. The CACQ database indexes were validated against pulmonary function test results of a sample of 71 randomly selected asthma patients. Patients were recruited from two asthma clinics and medical chart reviews were used to validate the CACQ database indexes against FEV_1 values [21].

The aim of this study was to systematically review the international literature to assess if the already existing algorithms are applied for the stratification of asthma patients according to disease severity based on available information in claims data. Furthermore, potential best practice standards are identified and their transferability to the German setting was discussed.

Methods

Data sources

A systematic literature review was performed in July 2015 using DIMDI SmartSearch—a search engine including several databases with a national and international scope, e.g. BIOSIS, MEDLINE, and EMBASE. The database search was performed on 1 July 2015 and included all publications present at that date in the included databases. An update of the search was performed on 24 September 2015. No further timely restrictions were applied. Additionally, a manual search was conducted to track references quoted by relevant articles. The review was limited to publications in the English and German languages. The systematic search was broadly defined to be able to identify a variety of publications. A three-step approach was used to identify publications that classified the severity of asthma by utilizing claims data. Asthma-specific publications were searched by focussing on publications mentioning the search term "asthma" in the abstract. English and German synonyms for claims data ("Abrechnungsdaten" eng. "administrative data" or "claims data", "Routinedaten" eng. "routine data", and "Sekundärdaten" eng. "secondary data") in full text search were used to identify relevant claims-data-based publications. Asthma-specific severity search terms were used in full text search ("schwer" eng."sever", "mild", "persistierend" eng. "persistent", "intermittierend" eng. "intermittent", and "moderat" eng. "moderate") to focus the search on disease severity. The detailed search algorithm is presented in Table 1.

The systematic search yielded a total of 640 publications, of which 335 were excluded as duplicates. Titles and abstracts of potential studies were separately screened by three independent reviewers. We excluded studies upfront that did not focus on asthma or did not use claims data. Publications were excluded if no full text was available, e.g. poster presentations and conference abstracts. Based on a full text review, studies were excluded if they did not apply an algorithm to distinguish between different disease severities or did not describe the methodology of identifying asthma disease severities.

Results

Asthma disease severity

The systematic research yielded 54 publications assessing asthma severity based on claims data (Fig. 1). Out of the 54 identified studies, 45 were conducted in the United States, 5 in Canada, 1 in Finland, 1 in Germany, 1 in New Zealand, and 1 in Puerto Rico. The identified studies were categorised based on the assessed asthma severity. Thirty-nine publications referred to either HEDIS criteria, Leidy criteria, the GINA guideline-based approach or the CACQ-based database indexes. An overview of the criteria of four specific algorithms that were applied throughout the publications is presented in Table 2.

As Table 3 shows, of the 39 publications, most of the identified studies (31 publications) used the HEDIS criteria to identify patients with persistent asthma. Of these, seven publications used the 2-year version, while 6 out of the 39 publications used a combination of three specific

Table 1 Systematic database search

No.	Search term	Results
[1]	ME05, BA05, EA08, EM05, GA03, GM03, IS05	45,263,126
[2]	AB = ?asthma?	199,791
[3]	FT = ?Abrechnungsdaten?	181
[4]	FT = ?Routinedaten?	522
[5]	FT = ?Sekundärdaten?	168
[6]	FT = ?routine data?	2767
[7]	FT = ?administrative data?	23,641
[8]	FT = ?secondary data?	10,396
[9]	FT = ?claims data?	23,272
[10]	[3] OR [4] OR [5] OR [6] OR [7] OR [8] OR [9]	58,780
[11]	FT = ?sever?	5,032,732
[12]	FT = ?mild?	684,188
[13]	FT = ?persistent?	417,821
[14]	FT = ?intermittent?	146,361
[15]	FT = ?moderate?	953,986
[16]	FT = ?schwer?	143,716
[17]	FT = ?persistierend?	3159
[18]	FT = ?intermittierend?	1891
[19]	FT = ?moderat?	981,340
[20]	[11] OR [12] OR [13] OR [14] OR [15] OR [16] OR [17] OR [18] OR [19]	6,476,060
[21]	[2] AND [10] AND [20]	640

ME05 MEDLINE, *BA05* BIOSIS Previews, *EA08* EMBASE Alert, *EM05* EMBASE, *GA03* gms, *GM03* gms Meetings, *IS05* SciSearch, *AB* search Abstract, *FT* search Freitext (engl. full text), *?* wildcard

algorithms, namely HEDIS 1-year, Leidy and GINA. As GINA only refers to asthma control it was not applied as single criteria whereas Leidy was applied in three studies. The CACQ database indexes were applied in five publications.

The use of HEDIS, Leidy and GINA was applied as a three-fold process. The six identified publications stated that HEDIS measures might mislabel mild intermittent asthma as mild persistent asthma, so additionally patients were required to meet the Leidy criteria [19]. Furthermore, Leidy and a GINA-guideline-based approach were then incorporated in conjunction into the algorithm for the confirmation of mild persistent asthma [6].

Sixteen publications applied a variety of different criteria for the severity categorisation and did not use the specific algorithms described above. Of these, 11 publications identified patients with a milder form of asthma that differentiated between classifying patients as "mild", "mild intermittent", and "intermittent". Seven publications identified patients with more severe forms of asthma. Distinctions were drawn between "persistent", "mild persistent", "moderate persistent", "severe persistent" and "severe" asthma. The different severity categories were assessed according to their own design. Out of the 16 publications, two studies investigated "low-risk" and "high-risk" asthma.

Table 4 presents an overview of the distribution of severities evaluated according to their own distinct definitions.

Based on the variety of assessed severities and the methods applied for their categorisation, all publications were stratified according to the determined severity.

Mild asthma

The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 493.0X, 493.1X, or 493.9X were applied throughout all publications as an appropriate tool for the inclusion of patients with asthma. Differences were linked to the number of claims being coded for each patient during the analysis. Friedman et al. [51] classified patients as having mild asthma based on no recorded exacerbations, which was defined as an asthma episode that required hospitalisation, an ED visit, or an outpatient visit in which patients received nebulised medication or an OCS prescription, and use of less than two canisters of inhaled SABA in the 6 month pre-index period. Patients were required to have at least one prescription for any dose of fluticasone/salmeterol (FPS) fixed dose combination, which was then considered the index date.

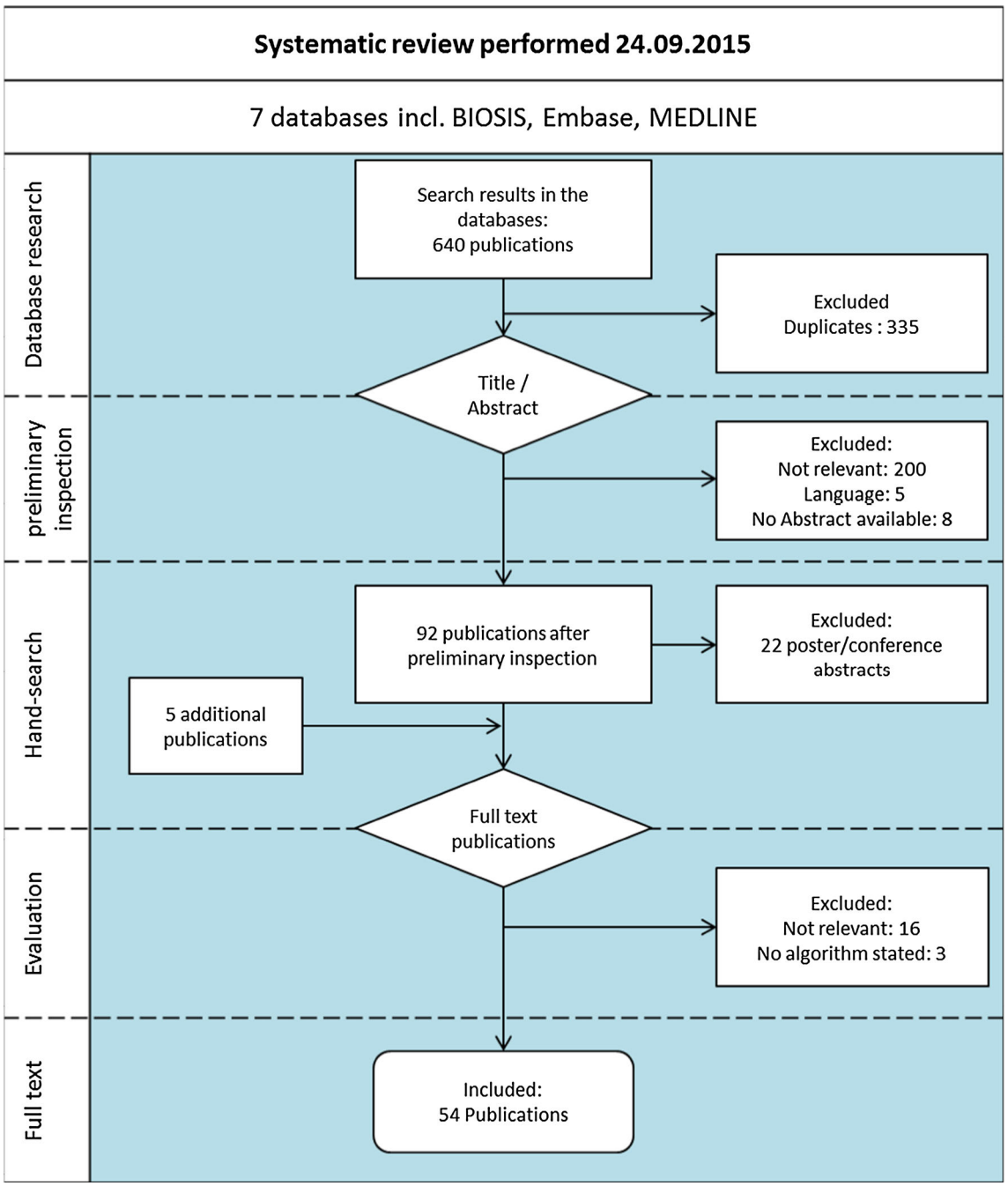

Fig. 1 Study selection

Another study from Friedman et al. [55] assessed mild asthma based on one index prescription of fluticasone propionate/salmeterol and no further ICS use. The authors determined severe persistent asthma extensively (see severe persistent asthma section of this paper) and considered patients as having mild asthma if none of the severe criteria was met.

In a study from Friedman et al. published in 2010 [49], all patients were required to be enrolled in a health plan for at least 1 year before and after the index date, which was defined as the first prescription fill of either mometasone furoate delivered through a dry powder inhaler or fluticasone propionate. Moreover, patients received no ICS/SABA combination therapy within 7 days of the index date. Patients were defined as having mild asthma if they had no asthma-related exacerbation, defined as described above, and less than three SABA canister claims during the pre-index period.

Table 2 Algorithms to identify asthma severity

Criteria/method	Description
HEDIS criteria	Persistent asthma: 12-month-period
	≥One acute inpatient hospitalisation with asthma as a primary diagnosis OR
	≥One ED visit with a primary asthma diagnosis OR
	≥Four claims for asthma prescription medications dispensed OR
	≥Four outpatient visits with asthma listed anywhere as one of the diagnosis AND
	≥Two claims for asthma prescription medications including quick-relief medications, controllers, biologic agents, and systemic corticosteroids
Leidy criteria	Mild intermittent asthma
	≤One inhaled β_2-agonist prescription and no oral steroid prescription per year
	Mild persistent asthma
	≤One inhaled β_2-agonist prescription and one oral steroid prescription per year OR
	Two or three inhaled β_2-agonist use per year and two oral steroid prescriptions per year OR
	Four to six inhaled β_2-agonist canister use per year and zero oral steroid prescriptions per year OR
	Moderate persistent asthma
	≤One inhaled β_2-agonist prescription and two oral steroid prescription per year
	Four to six inhaled β_2-agonist canister use per year and two oral steroid prescriptions per year OR
	>Six prescriptions of inhaled β_2-agonist per year and less than two oral steroid prescriptions per year
	Severe persistent asthma
	≤One inhaled β_2-agonist prescription and more than two oral steroid prescriptions per year
	Two or three inhaled β_2-agonist use per year and more than two oral steroid prescriptions per year OR
	Four to six inhaled β_2-agonist canister use per year and more than two oral steroid prescriptions per year OR
	>Six prescriptions of inhaled β_2-agonist per year and more than one oral steroid prescriptions per year
GINA criteria	Mild persistent asthma
	Low dose ICS
	Moderate persistent asthma
	Medium dose of ICS OR
	Low-medium dose ICS with LABA
	Severe persistent asthma
	High-dose ICS with or without LABA
CACQ database indexes	Mild asthma
	0–500 μg ICS per day, no other controller therapy, 0–3 doses of SABA per week, no moderate to severe exacerbations[a]
	0–250 μg ICS per day, further controller therapy, 0–3 doses of SABA per week, no moderate to severe exacerbations[a]
	0–500 μg ICS per day, no other controller therapy, 0–3 doses of SABA per week, moderate to severe exacerbations[b]
	0–250 μg ICS per day, further controller therapy, 4–10 doses of SABA per week, no moderate to severe exacerbations[b]
	0–500 μg ICS per day, no other controller therapy, 4–10 doses of SABA per week, no moderate to severe exacerbations[b]
	Moderate asthma
	251–500 μg ICS per day, further controller therapy, 0–10 doses of SABA per week, no moderate to severe exacerbations[a]
	501-1000 μg ICS per day, 0–10 doses of SABA per week, no moderate to severe exacerbations[a]
	>1000 μg ICS per day, 0–3 doses of SABA per week, no moderate to severe exacerbations[a]
	0–250 μg ICS per day, further controller therapy, 4–10 doses of SABA per week, moderate to severe exacerbations[b]
	0–500 μg ICS per day, no other controller therapy, 4–10 doses of SABA per week, moderate to severe exacerbations[b]
	0–250 μg ICS per day, further controller therapy, >10 doses of SABA per week, no moderate to severe exacerbations[b]
	0–500 μg ICS per day, no other controller therapy, >10 doses of SABA per week, no moderate to severe exacerbations[b]
	251–500 μg ICS per day, further controller therapy, >10 doses of SABA per week, no moderate to severe exacerbations[b]
	251–500 μg ICS per day, further controller therapy, 0–10 doses of SABA per week, moderate to severe exacerbations[b]
	501–1000 μg ICS per day, >10 doses of SABA per week, no moderate to severe exacerbations[b]
	501–1000 μg ICS per day, 0–10 doses of SABA per week, moderate to severe exacerbations[b]

Table 2 continued

Criteria/method	Description
	Severe asthma
	Controlled
	>1000 μg ICS per day, 4–10 doses of SABA per week, no moderate to severe exacerbations[a]
	0–1000 μg ICS per day, >10 doses of SABA per week, moderate to severe exacerbations[b]
	>1000 μg ICS per day, 0–10 doses of SABA per week, moderate to severe exacerbations[b]
	>1000 μg ICS per day, >10 doses of SABA per week[b]

HEDIS Healthcare Effectiveness Data and Information Set, *CACQ* Canadian Asthma Consensus Guidelines, *GINA* Global Initiative for Asthma, *ICS* inhaled corticosteroid, *LABA* long-acting beta-agonist, *SABA* short-acting β_2 agonist

[a] Controlled

[b] Uncontrolled

In a study by Friedman et al. [50], patients were required to be enrolled on their health plan for at least 1 year before and after their index date, and with no prior claims for asthma exacerbation. The index date was defined as a first claim for either mometasone furoate or beclomethasone dipropionate prescription. The classification of mild asthma was made based on less than three SABA canister claims and no asthma exacerbation, defined as an asthma episode that required hospitalisation, an ED visit, or an outpatient visit with nebulised medication or a prescription for OCS, within 12 months prior to index date.

Navaratnam et al. [54] defined mild asthma as less than or equal to two SABA canister claims and no exacerbation, which was defined as an asthma episode that required hospitalisation, an emergency department visit, or an outpatient visit with nebulised medication or an OCS prescription, during the pre-index period. Patients were required to be enrolled at least 1 year prior and after the index date, which was defined as the first prescription for mometasone furoate or fluticasone propionate with salmeterol. The same criteria were applied in further studies published by Navaratnam et al. [52, 53].

Erickson et al. [43] defined mild asthma based on the Leidy criteria for "mild intermittent" asthma and "mild" asthma using a method described by Cai et al. [64]. Mild intermittent asthma is defined as one or less canisters of an inhaled β-agonist within 12 months, and mild asthma as five or less prescriptions of inhaled or oral β-agonist, a theophylline compound, inhaled ipratropium bromide, or an anti-allergic compound (cromolyn, nedocromil or ketotifen).

Mild intermittent asthma

Gillies et al. [56] defined four asthma treatment groups with a diagnosis of asthma. Three steps were described, adopted from the British Guideline of the Management of Asthma. Step 1, mild intermittent asthma, was defined by at least two SABA inhalers dispensed in a 12-month period. Step 2 and 3 comprised a more severe form of asthma and the corresponding treatment.

Guo et al. [57] divided asthma severity into four levels: mild intermittent, mild persistent, moderate persistent, and severe persistent asthma. Patients were identified based on an asthma diagnosis indicated by an ICD-9 Code 493.xx from an institutional or medical claim. The severity assessment was based on the recommended drug regimens from 2002 National Asthma Education and Prevention Program (NAEPP) guidelines update to Expert Panel Report 2 (EPR-2). All patients were required to have a SABA prescription. Whereas patients identified as mild intermittent did not have any claims for an ICS.

Intermittent asthma

Jacob et al. [58] stratified patients into two mutually exclusive groups of patients with intermittent or persistent asthma. The stratification was based on prescribed asthma medication. Asthma patients were identified by ICD-10-GM codes. All asthma patients without any evidence of asthma medication and those with a record of reliever medication (i.e. at least one prescription of a short acting b2-agonist) were classified as intermittent asthma, if they had no record of an asthma-related hospitalisation in the study period.

Moderate asthma

Erickson et al. [43] defined moderate asthma based on drugs dispensed within 12 consecutive months. Referring to the frequency of pharmacy claims for multiple combinations of reliever and controller medications, subjects were required to have four to six prescriptions (or canisters) of inhaled β-2 agonist, and/or two prescriptions of oral steroids. Furthermore, patients were classified as moderate if they did not meet the criteria for mild or severe asthma.

Table 3 Overview of the studies referring to algorithms (Methods/ criteria) to identify asthma severity

Reference	HEDIS 1-year	HEDIS 2-year	Leidy	GINA	CACG
Andrews et al. [22]	X				
Baxter et al. [23]	X				
Berger et al. [18]	X				
Broder et al. [9]	X				
Cabana et al. [24]	X				
Canino et al. [25]	X				
Dombkowski et al. [26]	X				
Finkelstein et al. [27]	X				
Fuhlbrigge et al. [28]	X				
Hsu et al. [29]	X				
Mosen et al. [30]	X				
Richardson et al. [31]	X				
Schatz et al. [32]	X				
Schatz et al. [33]	X				
Schatz et al. [34]	X				
Schatz et al. [8]	X				
Wakefield & Cloutier [35]	X				
Wilson et al. [36]	X				
Birnbaum et al. [6]	X		X	X	
Colice et al. [37]	X		X	X	
Colice et al. [38]	X		X	X	
Colice et al. [10]	X		X	X	
Ivanova et al. [39]	X		X	X	
Ivanova et al. [40]	X		X	X	
Dombkowski et al. [14]		X			
Schatz and Zeiger [11]		X			
Schatz et al. [17]		X			
Vernaccio et al. [15]		X			
Yong and Werner [12]		X			
Yoon et al. [13]		X			
Zeiger et al. [16]		X			
Allen-Ramey et al. [42]			X		
Erickson et al. [43]			X		
Wells et al. [44]			X		
Blais and Beauchesne [45]					X
Blais et al. [46]					X
Blais et al. [47]					X
Firoozi et al. [21]					X
Firoozi et al. [48]					X

Persistent asthma

Jacob et al. [58] identified patients with persistent asthma by using medication claims for long-acting β-2 agonists (LABA), leukotriene modifiers (LTRA), inhaled corticosteroids, oral corticosteroids, Anti-IgE, theophylline, and ipratropium bromide in combination with hospitalisations with a primary diagnosis of asthma. Patients were classified as having persistent asthma if they had one or more of the mentioned medication claims, or an asthma-related hospitalisation.

Rust et al. [59] assessed patients with at least one inpatient or two outpatient claims for asthma in 2007. Only children aged 5–12 years with an initial claim for an inhaled corticosteroid prescription were included. The initial claim was defined by no record of long-term control prescription drug claims, including inhaled corticosteroids, leukotriene inhibitors and oral corticosteroids, in the

Table 4 Evaluated severities of asthma

Reference	Mild	Mild Inter-mittent	Inter-mittent	Moderate	Persistent	Mild Persistent	Moderate Persistent	Severe Persistent	Severe	Low-risk	High-risk
Friedman et al. [49]	X										
Friedman et al. [50]	X										
Friedman and Yawn [51]	X										
Navaratnam et al. [52]	X										
Navaratnam et al. [53]	X										
Navaratnam et al. [54]	X										
Erickson et al. [43]	X			X					X		
Friedman et al. [55]	X								X		
Gillies et al. [56]		X									
Guo et al. [57]		X				X	X	X			
Jacob et al. [58]			X		X						
Rust et al. [59]					X						
Vaidya et al. [60]					X						
Wertz et al. [61]							X	X			
Klemets et al. [62]										X	X
Talbot et al. [63]										X	X

90 days prior to the initial claim with ICS. Children with their initial ICS claim during the period from 1 April 2007 to 30 September 2007 were staged as "persistent" or described as having asthma of sufficient severity and persistence to require ICS as a long-term controller medication. More severe asthma was defined by drug claims for two or more SABA rescue inhalers within the 90-day period prior to initial ICS prescription. The use of SABA was found to be one of the strongest predictors of asthma-related ED visits among patients who met HEDIS criteria for persistent asthma.

Vaidya et al. [60] referred to patients receiving controller therapy by assessing the prescription drug records, which were required to include at least one claim for inhaled corticosteroids, cromolyn, or montelukast, and were coded between June 2006 and June 2007. Based on an ICD-9-CM code 493.xx in the primary or secondary diagnosis field, subjects with persistent asthma were identified from the outpatient claims from January 2006 to December 2007. The first claim for controller medication was considered the index date, and the 6 months before and after were assessed in the study.

Mild persistent asthma

Guo et al. [57] identified mild persistent asthma in two groups of patients based on pharmaceutical use. Patients below the age of 5 years were classified as mild persistent by medication regimens over a period of at least 90 days after the asthma index date. Mild persistent asthma included use of SABA, low dose ICS, mast cell stabilizer or leukotriene modifier as an alternative treatment to ICS. Patients above the age of 5 years were classified as mild persistent similar to the drug regimens of children younger than 5 years with the addition of Theophylline as an alternative to ICS treatment.

Moderate/severe persistent asthma

Guo et al. [57] identified moderate persistent asthma patients by the use of asthma medication within a timeframe of at least 90 days. Patients receiving SABA, low dose of ICS, LABA, leukotriene modifier, and/or Theophylline therapy were classified as moderate persistent asthma patients.

Wertz et al. [61] identified moderate to severe asthma based on at least one medical claim for asthma ICD-9-CM code 493.xx, and at least one pharmacy claim for an asthma controller medication, defined by an Expert Panel [38], such as inhaled corticosteroid monotherapy, leukotriene antagonist, or inhaled corticosteroid combination, between 1 September 2005, and 31 August 2006.

Severe persistent asthma

Guo et al. [57] identified severe persistent asthma patients by the use of asthma medication within a timeframe of at least 90 days. Patients receiving oral corticosteroids besides their SABA, ICS and/or LABA therapy were classified as severe persistent asthma patients.

Severe asthma

Erickson et al. [43] observed a variation in the distribution of health-related quality of life and work performance scale scores based on different methods of determining asthma severity. An asthma service claim with a prescribed asthma medication or a claim for two asthma medication prescriptions in the 18 months prior to the survey were considered the basic inclusion criteria for patients with moderate to severe asthma, followed by multi drug use. Multi drug use was defined to categorize severe asthma. If subjects received any of the following groupings in a period of 12 consecutive months before the survey, they were considered to have severe asthma:

- Group 1: at least six canisters or prescriptions of any bronchodilators (inhaled, oral or nebulised β-agonist, theophylline, ipratropium) and at least six more prescriptions for an inhaled corticosteroid or anti-allergic compound
- Group 2: at least three prescriptions in each of at least three different classes of asthma medication, the classes being β-agonist, theophylline, anti-allergic, ipratropium bromide, corticosteroids whether inhaled or oral
- Group 3: at least 2 prescriptions for oral corticosteroids and six or more prescriptions for any other asthma medication
- Group 4: at least 25 canisters of a β-agonist bronchodilator [43].

Friedman et al. [55] classified asthma as severe disease if patients met one of the following criteria within 1 year: one or more claims for an ICS, >365 doses of albuterol from an inhaler or >365 inhalation unit doses of albuterol or levalbuterol, one or more claims for oral corticosteroids (OCSs), an asthma related visit in urgent-care (UC) or in an ED followed by a prescription for an OCS within 7 days of the visit, or a hospital admission for asthma.

High-risk asthma

High risk asthma was defined by Klemets et al. [62] as a record of at least one asthma related hospitalisation with an ICD code in primary position in a period of 12 months. Talbot et al. [63] modified the definition by adding asthma-related visits to emergency departments and prescriptions of corticosteroids as rescue therapy or long-term courses of oral corticosteroids or prescriptions for three or more β-agonists during the course of 1 year to classify individuals as high-risk asthma patients. Both Klemets et al. and Talbot et al. defined low-risk asthma as not meeting the criteria for high-risk asthma [62, 63].

Table 5 gives an overview of the different severity criteria used in the identified publications. Each of the 16 identified publications not using one of the established algorithms were grouped according to the applied algorithm in terms of the criteria they used to classify asthma severity. The established algorithms were represented by Schatz et al. for HEDIS, Erickson et al. applying Leidy, Birnbaum et al. for GINA, and Firoozi et al. for CACQ [6, 8, 21, 43].

Discussion

The systematic literature search yielded 54 publications that evaluated asthma severity based on claims data, despite the fact that clinical data is missing in this data source [40]. Different approaches have been developed over the last two decades to overcome this limitation. Previous work has shown that claims-data-based instruments are feasible to assess quality-of-care [33], and that algorithm-based severity categorisation is possible [6]. Claims data analyses provide relevant observational information for a large number of patients, reflecting real-life treatment patterns [40, 66]. The reviewed literature suggests that previously described algorithms such as HEDIS, Leidy and CACG are used widely but no best practice for the identification of disease severity in asthma patients using claims data has been established so far. Also, the HEDIS criteria was applied in 31 publications, but a more differentiated look at the most recent publications indicates that alternatives are still of interest. In the timeframe of the most recent 5 years (2011–2015), six publications used the HEDIS criteria whereas five publications used other algorithms. Expanding the timeframe to the most recent 6 years shifts the result in favor of other algorithms than HEDIS (11 other vs. 10 HEDIS). HEDIS relies on asthma claims coded at ED visits, hospitalisations, outpatient visits, or SABA prescription fills, which is a commonality also found in Leidy's algorithm. As Birnbaum et al. [6] state, this medication-derived method can

Table 5 Severity criteria of asthma

Criteria	Mild	Mild Intermittent	Intermittent	Moderate	Persistent	Mild Persistent	Moderate Persistent	Severe Persistent	Severe	Low-risk	High-risk
SABA	[49] [21,50-55]	[56,57]	[58]	[21]	[58, 59]	[57]	[57]	[57]	[21]	[63]	
LABA					[58]	[6, 57]	[6, 57]	[6, 57]			
inhaled β-2 agonist	[43]	[43]			[58]	[43]	[43]	[43]	[43]	[63]	[63]
ICS	[21]			[21] [61]	[58] [59, 60]	[6, 57]	[6, 57]	[6] [57]	[21, 43, 61]		[63]
OCS	[21]			[21]	[58]	[43]	[43]	[43, 61]	[21, 43]		[63]
Anti-IgE					[58]						
Theophylline	[43, 65]				[58]		[57]		[43, 65]		
Leukotriene modifier				[61]	[58]	[57]	[57]		[61]		
Ipratropium bromide	[43, 65]				[58]				[43]		
Mast cell stabilizer					[60]	[57]					
Other controller medication	[21]			[21]							
Any Asthma medication					[8]				[43]		
Anti-allergic compound	[43]								[43]		
Outpatient visits					[8]						
No outpatient visits with nebulized medication or OCS prescription	[49-55]										
ED	[21]			[8]					[21]		[62, 63]
No ED	[49-55]									[62, 63]	
Hospitalization	[21]			[21]	[58]				[21]		[62, 63]
No hospitalization	[49-55]		[58]							[62, 63]	
No ICS, OCS,										[63]	

categorise patients as having more severe asthma than the symptom-derived methods based on clinical data. An analysis in children with asthma suggested that HEDIS criteria for persistent asthma is very sensitive, but has relatively low specificity; hence, it might misclassify patients with intermittent asthma as having persistent asthma [67]. To avoid this possible misclassification, Leidy's criteria was applied to exclude patients who might have intermittent asthma, by incorporating minimal requirements for the number of SABA claims to be identified as persistent. Thus, Leidy's algorithm is commonly used as an additional secondary screen to the HEDIS criteria, when classifying patients with mild persistent asthma [10]. The claims-data-based GINA criteria—an approach used in combination with HEDIS and Leidy—provides recommendations based on the daily dose of ICS and LABA, but is less specific than HEDIS and Leidy when comparing the requirements for asthma medication use based on claims data. However, the GINA guideline is considered the gold standard in clinical practice for the assessment of disease control. In contrast, Leidy's criteria refers only to SABA use, which does not include inhaled corticosteroids, present in the former GINA guideline [20]. The CACQ database indexes were used as standalone classification for asthma severity, also incorporating asthma control. These indexes use a comprehensive matrix of criteria, including daily ICS dose, weekly SABA dose, other controller medication and markers of moderate/severe exacerbations to assess asthma severity [21]. Thus, they are more complex then HEDIS, LEIDY and GINA. So far a validation for HEDIS, Leidy and CACQ is warranted.

One objective of this review was the evaluation of a potential replication of the identified algorithms to the German setting. Most of the studies presented here were conducted in the United States, where a different health care system and coding system is in place, which makes the assessment of a possible transfer to a German setting even more important. Claims data from the German Statutory Health Insurance are collected primarily for the purpose of reimbursement and documentation. Clinical data, and also information about the intention of the physician, e.g. prescribed dosage and frequency, is missing. This limits the potential of dosage-based classifications such as the GINA-based approach.

In Germany, information on diagnosis in the outpatient sector is given only on a quarterly basis. In contrast, medical services are recorded on a daily basis. Therefore, it is not possible to exactly match a diagnosis with a specific outpatient visit. The limitation also takes effect on the identification of outpatient emergency cases [7]. To apply the HEDIS criteria to German claims data is not completely possible due to the quarterly documentation of outpatient diagnoses. Each diagnosis is only recorded once a quarter for every physician the patient consulted. Especially, the identification of at least four outpatient visits with asthma listed as a diagnosis poses a challenge, since a patient would be required to have an outpatient claim in each quarter or with different physicians to amount to four claims for asthma. Furthermore, the analysis of an emergency case with an asthma diagnosis is possible only for the inpatient setting. Emergency cases in the outpatient setting might be misclassified in terms of multi-morbid patients, due to the quarterly documentation of outpatient diagnoses.

Leidy's criteria assess asthma based on requirements for the amount of asthma-specific prescriptions per year. Mild persistent asthma is defined by four to six SABA refills and zero oral OCS prescriptions per year or two to three SABA refills and less than two OCS prescriptions per year. This specific algorithm can be applied to German claims data, as the medication prescriptions are documented and can be assessed.

The former GINA guideline provides recommendations for categorising mild or severe persistent asthma based on the daily dose of inhaled corticosteroids and at least a second controller, i.e. LABA, LTRA, Theophylline, and OCS. These criteria cannot be transferred to German claims data without inaccuracy, as the daily dose can only be estimated. The data does not include prescribed dosage information, which might modify the use of ICS and salmeterol in a specific case [7].

The studies that did not refer to the algorithms mentioned above were categorized based on the severity assessed. In total, 16 publications were stratified to mild, mild intermittent, intermittent, moderate, persistent, mild persistent, moderate persistent, severe persistent, severe and low/high-risk asthma. The basis for the inclusion of persistent asthma patients were mostly asthma service claims. The publications varied especially in specificity concerning the amount of prescriptions for asthma specific medication and where asthma claims needed to be coded, i.e. inpatient or outpatient sector, or ED visit [43, 55, 61]. Publications assessing mild asthma with various criteria excluded asthma exacerbations, mostly defined as an asthma episode that required hospitalisation, an emergency department visit, or an outpatient visit in which patients received nebulised medication or a prescription for OCS. Moreover, similar to the partly medication-derived algorithms from HEDIS and Leidy, asthma-specific medication, or an overreliance on SABA, were considered an indication for a higher asthma severity [49–51, 55]. Publications determining moderate to severe persistent asthma focussed on asthma-specific medication, such as fluticasone propionate/salmeterol, albuterol, and levalbuterol, which are β_2-agonists. Furthermore, the number of prescription fills for inhaled corticosteroids was considered an important identification criterion for more severe asthma [43, 55].

The evaluation of methods applied suggests that asthma severity in administrative data is connected with claims for asthma and asthma-specific medication, varying by the type of therapy received. Claims for oral or inhalative corticosteroids are associated with higher disease severity, whereas mild asthma is associated mostly with restricted use of short-acting β_2-agonists.

Due to the fact that the identified algorithms have commonalities with the specific algorithms from HEDIS and Leidy, transfer to the German context is possible with a few restrictions. As already mentioned, physician contacts and emergency cases in the outpatient setting cannot be accurately connected to a specific ICD-10-GM diagnosis code. Furthermore, the severity categorisation based on medication use can be applied if the use does not refer to daily doses but instead to the number of prescriptions. It should be noted that claims for prescriptions dispensed can be imprecise as the data identifies only that a canister was dispensed by a pharmacy—regardless of whether the medication was actually used by the patient [27].

Conclusion

The results of this systematic review suggest that there is no best practice method for the categorisation of asthma severity grades with claims data. Also, although HEDIS is used in the majority of studies, this is more heterogeneous for the most recent publications (2010–2015). Rather, a combination of the specific algorithms seems to be a pragmatic approach. Furthermore, it should be noted that, by the date of the systematic search, only one study was identified that used a study design similar to the German context. The analysis of the specific algorithms indicates some limitations, which might lead to a misclassification of asthma severity if only a single algorithm is applied. A factor common to the assessed algorithms, both specific and unspecific, is that they refer to either asthma-specific medication and/or claims in the inpatient or outpatient sector. It should be noted that the studies vary in the amount of necessary prescriptions for asthma specific-medication and claims in the inpatient or outpatient sector. The transfer to a German context is not entirely possible without considering particular conditions associated with German claims data, especially in the outpatient sector. Nevertheless, as claims data has important advantages based on the observational information for a large number of patients, which also accurately reflects the resource use and costs of a disease, these algorithms could be modified and applied to the German setting and provide an approach for a health economic evaluation.

Compliance with ethical standards

Conflict of interest The study was funded by an unrestricted grant from GlaxoSmithKline. Benno Bechtel is an employee of GlaxoSmithKline. Jennifer Scarlet Haas, Christian Jacob and Sebastian Braun are employed by Xcenda GmbH, which received funding for the conduct of the study from GlaxoSmithKline. Peter Kardos received consulting fees for the conduct of the study from Xcenda GmbH.

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Modul 6

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ORIGINAL RESEARCH ARTICLE

Retrospective analysis into differences in heart failure patients with and without iron deficiency or anaemia

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Abstract

Aims The aim of this study was to assess the burden of heart failure (HF) patients with/without iron deficiency/iron deficiency anaemia (ID/A) from the health insurance perspective.

Methods and results We conducted a retrospective claims database analysis using the Institut für angewandte Gesundheitsforschung Berlin research database. The study period spanned from 1 January 2012 to 31 December 2014. HF patients were identified by International Statistical Classification of Diseases and Related Health Problems, 10th revision, German Modification codes (I50.-, I50.0-, I50.00, I50.01, I50.1-, I50.11, I50.12, I50.13, I50.14, I50.19, and I50.9). HF patients were stratified into HF patients without ID/A and HF patients with ID/A (D50.-, D50.0, D50.8, D50.9, and E61.1). HF patients with ID/A were stratified into three subgroups: no iron treatment, oral iron treatment, and intravenous iron treatment. A matching approach was applied to compare outcomes for HF patients without ID/A vs. HF patient with untreated incident ID/A without iron treatment and for HF patients receiving no iron treatment vs. oral iron treatment vs. intravenous iron treatment. Matching parameters included exact age, sex, and New York Heart Association functional class. An optimization algorithm was used to balance total health care costs in the baseline period for the potential matched pairs without sample size reduction. In total, 172 394 (4537.4 per 100 000) HF patients were identified in the Institut für angewandte Gesundheitsforschung Berlin research database in 2013. Of these, 11.1% (19 070; 501.9 per 100 000) were diagnosed with ID/A and/or had a prescription for iron medication in 2013. The mean age of HF patients was 77.0 years (±12.0 years). Women were more frequently diagnosed with HF (54.6%). HF patients with untreated incident ID/A (1.77%) had a significantly higher all-cause mortality than HF patients without ID/A (33.1% vs. 24.1%, $P < 0.01$). The analysis of health care utilization revealed significant differences in the rate of all-cause hospitalization (72.9% vs. 50.5%, $P < 0.01$). The annual health care costs for HF patients with untreated incident ID/A amounted to €17 347 with incremental costs of €849 ($P < 0.01$) attributed to ID/A.

Conclusions Heart failure is associated with a major burden for patients and the health care system in terms of health care resource utilization, costs, and mortality. Our findings suggest that there is an unmet need for treating more HF patients with ID/A with iron medication.

Keywords Claims data; Heart failure; Iron deficiency anaemia; Statutory health insurance; Cost of illness

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Introduction

Heart failure (HF) is a clinical syndrome presenting with typical symptoms like breathlessness, ankle swelling, and fatigue. These symptoms might be accompanied by signs of elevated jugular venous pressure, pulmonary crackles, and peripheral oedema. HF is caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or an elevated intracardiac pressure when the patients are at rest or during phases of stress.[1] HF appears in different stages that are classified according to the New York Heart Association (NYHA) into four functional classes NYHA I to NYHA IV describing the severity of symptoms and exercise tolerance.[2] Approximately 800 000 to 1 600 000 individuals of the German population are affected by HF[3] with a prevalence of

3956.3 per 100 000 and an incidence of 270–655 per 100 000[4] and differ among federal states in Germany.[5,6] HF is associated with an increased mortality and was the third most common reason for death in Germany in 2015 with 47 414 cases and 5.1% of all deceased.[7] Iron deficiency anaemia (ID/A) has been reported as a frequent co-morbidity in chronic HF in up to 50% and has been associated with impaired functional capacity, poor quality of life, and increased mortality,[8–11] whereas all-cause anaemia alone has been reported in congestive HF patients in up to 17%.[12] Treating HF patients with ID/A with intravenous iron supplement treatment improves symptoms, functional capacity, and quality of life.[13,14] For patients with systolic HF and ID receiving intravenous iron supplement treatment also a reduction of recurrent cardiovascular (CV) and HF-related hospitalizations and all-cause and CV mortality was reported.[15]

Nevertheless, little is known about the burden of ID/A in HF patients from a health care system/payer perspective. So far, health care utilization—in terms of hospitalizations and outpatient visits, as well as corresponding health care expenditures—has not been investigated for HF patients with and without ID/A, taking into account the broad spectrum of sectors in a health care system.

The aim of this study was to provide current information on the prevalence of HF in Germany and to further assess the incremental burden of ID/A in patients suffering from HF from the perspective of the statutory health insurance (SHI). Moreover, this study compared the effect of intravenous iron treatment vs. oral iron treatment or no iron treatment in HF patient suffering from ID/A.

Methods

Study design

We conducted a retrospective claims database analysis using the Institut für angewandte Gesundheitsforschung Berlin (InGef) research database (formerly known as Health Risk Institute research database) containing anonymized health care claims of approximately four million covered lives. The InGef research database is adjusted to the German population in terms of age and gender and is considered to be in good accordance with the German population for measures of morbidity, mortality, and drug usage.[16] The study was conducted from the perspective of the SHI.

Data source

Legal basis/foundation

The InGef research database includes verified claims data of the participating insurance companies, which is originally used for reimbursement purposes. These claims data were used in this study for scientific research purposes in accordance with German Social Law.

Data protection

The InGef research database addresses all data protection regulations in Germany. All personal information of patients, physicians, and other health care providers is anonymized before the data are made available for research. Results will not be reported for groups with less than five patients.

Data flow

The InGef database consists of claims data from approximately 75 different health insurances corresponding to approximately two-thirds of the overall number of health insurances in Germany. The InGef research database is an adjusted sample of the pooled claims data of the participating health insurances and covers approximately four million lives, structured to represent the German population in terms of age and gender as of 2013.

Study period

The study period encompasses the time frame from 1 January 2012 to 31 December 2014.

Study population

Heart failure patients were identified by using International Statistical Classification of Diseases and Related Health Problems, 10th revision, German Modification (ICD-10-GM) codes (Heart failure I50.-, Right ventricular failure I50.0-, Primary right ventricular failure I50.00, Secondary right ventricular failure I50.01, Left ventricular failure I50.1-, Left ventricular failure, NYHA functional class I I50.11, Left ventricular failure, NYHA functional class III 50.12, Left ventricular failure, NYHA functional class III I50.13, Left ventricular failure, NYHA functional class IV I50.14, Left ventricular failure, unspecified I50.19, Heart failure, unspecified I50.9) in the inpatient (main or secondary diagnoses) and/or outpatient setting (verified diagnoses) from 1 January 2013 to 31 December 2013.

Subgroups

Heart failure patients were stratified into HF patients without ID/A and HF patients with ID/A using ICD-10-GM codes [Iron deficiency anaemia D50.-, Iron deficiency anaemia secondary to blood loss (chronic) D50.0, Other iron deficiency anaemias D50.8, Iron deficiency anaemia, unspecified D50.9, Iron deficiency E61.1] for ID/A and/or Anatomical Therapeutic Chemical Classification System (ATC) codes for prescribed iron medication (B03A) in the time frame from 1 January 2013 to 31 December 2013.

An index quarter was defined for each group. For HF patients without ID/A, the index quarter was defined by the first HF diagnosis in 2013. For HF patients with ID/A, the first quarter in 2013 with either both an HF diagnosis and an iron prescription or both an HF diagnosis and an ID/A diagnosis determined the index quarter.

To assure that HF patients without ID/A were not misclassified, they additionally were screened for ID/A codes in the four quarters before the index quarter and in the three quarters after the index quarter.

Furthermore, HF patients with ID/A were stratified into three subgroups: no iron treatment, oral iron treatment, and intravenous iron treatment. Oral iron treatment was identified by ATC codes B03AA and B03AB for oral preparations and B03AD and B03AE for oral combinations of iron and other agents. Intravenous iron treatment was identified by ATC codes B03AC for parenteral iron preparations.

To ensure that patients in the no iron treatment group were treatment naïve and were not treated with iron throughout the entire individual observation period, patients having a prescription of iron in the four quarters before the index quarter or starting an iron treatment in the three quarters after the index without a concurrent HF diagnosis were excluded from this group.

To be able to compare HF patients with oral iron treatment and intravenous iron treatment, only patients who were incident on iron treatment and did not switch the iron treatment were included in the analysis. Therefore, patients who either had a prescription of iron in the four quarters before the index quarter or who switched between oral and intravenous iron in the index quarter or the three subsequent quarters were excluded from these two groups.

Patients were described in terms of age and sex at the index quarter. They were stratified into NYHA functional classes using the highest NYHA functional class coded by ICD-10-GM in the index quarter. NYHA functional class I was identified by ICD-10-GM code I50.11, NYHA functional class II was identified by ICD-10-GM code I50.12, NYHA functional class III was identified by ICD-10-GM code I50.13, and NYHA functional class IV was identified by ICD-10-GM code I50.14. HF patients with no specific NYHA functional class code in 2013 (I50, I50.0, I50.00, I50.01, I50.1, I50.19, and I50.9) were classified as NYHA functional class N/A.

Matching

An exact direct 1:1 matching approach was used to compare HF patients without ID/A with HF patients with untreated incident ID/A. Matching parameters were age, sex, and NYHA functional class. Total health care costs in the four quarters before the index quarter (baseline period) were balanced using an optimization algorithm. In cases where there were various matching partners available for an HF patient with incident ID/A, the optimization algorithm chose the individual that in total overall matched pairs minimized the costs difference of total health care costs in the four quarters before the index quarter.

An exact direct 1:1:1 matching approach was used to compare HF patients with ID/A receiving no iron treatment with HF patients with ID/A who were treated with oral iron medication and with HF patients with ID/A who were treated with intravenous iron medication. Matching parameters were age classes of 5 years, sex, and NYHA functional class. Total health care costs in the four quarters before the index quarter were balanced using an optimization algorithm. In cases where there were various matching partners available, the optimization algorithm chose the individual that in total overall matched pairs minimized the costs difference of total health care costs in the four quarters before the index quarter (baseline period).

Matching balance was measured by the standardized difference with a threshold of 10%[17–20] indicating an imbalance of the matching parameters if the standardized difference exceeds the threshold.

Patients with the need of dialysis in the baseline period were excluded before the matching as dialysis-dependent ID/A was not the subject of this study.

Mortality

All-cause mortality was analysed in an individual 1 year time frame of four quarters including the index and the following three quarters. All-cause mortality was described as an annual rate, and Kaplan–Meier estimators were used to determine time to death. Differences in the all-cause mortality between the groups were tested with log-rank tests for statistical significance. All-cause mortality was defined as any reason for death as the utilized data source contains no explicit reason for death for each patient.

Outcomes

Health care utilization and costs were assessed in an individual 1 year time frame including the index quarter and the following three quarters. Hospitalizations were analysed in terms of all-cause hospitalizations and HF-related hospitalization, defined as hospitalizations with an HF diagnosis recorded as the main or secondary diagnosis. Outpatient visits were considered to be HF related if an HF diagnosis was coded as a verified diagnosis in the same quarter. Sick leave was analysed in relation to HF, defined as all cases of sick leave with an HF diagnosis, and overall. Health care costs were analysed in total and for the cost domains inpatient care, outpatient care, pharmaceuticals, devices and aids, and sick leave payments. Health care costs were separately analysed for HF patients deceasing in the 1 year time frame and those surviving it.

Results

Descriptive unadjusted analyses

Study population

The InGef research database encompassed 3 799 392 individuals who were continuously observable in the years 2012 to 2014 with exception of individuals who deceased in 2013 or 2014. This sample served as the basis of the analysis.

Prevalence

In total, 172 394 (4537.4 per 100 000) HF patients were identified in the InGef research database in 2013. Extrapolated to the German population, this would result in a total of approximately 3 653 691 individuals and 3 159 716 individuals for the SHI population.[21,22] Of these, 11.1% (19 070; 501.9 per 100 000) were also diagnosed with ID/A and/or had a prescription for iron medication in 2013. ID alone was documented in only 0.9% of the HF patients (1529 patients).

Demographics and New York Heart Association functional classes

The mean age of HF patients was 77.0 years (±12.0 years) for both sexes and all NYHA functional classes. Patients with NYHA functional class IV were on average older (79.3 ± 10.8 years) than patients with other NYHA functional classes (NYHA I: 72.2 ± 13.0 years, NYHA II: 75.1 ± 11.6 years, NYHA III: 77.7 ± 11.2 years, and NYHA N/A: 77.2 ± 12.2 years). Women with HF (54.6%) were on average older than male HF patients overall NYHA functional classes, ranging from 74.8 ± 12.8 years in NYHA functional class I to 82.0 ± 9.8 years in NYHA functional class IV. In comparison, men with HF had a mean age of 74.0 ± 12.0 years, ranging from 69.9 ± 12.7 years in NYHA functional class I to 76.5 ± 11.0 years in NYHA functional class IV.

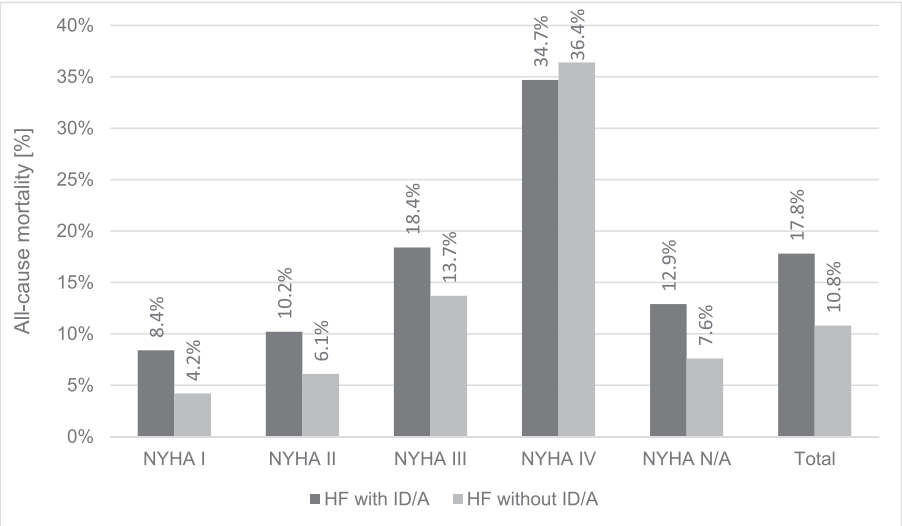
The mean age of HF patients with ID/A was 79.1 ± 10.9 years in contrast to 76.7 ± 12.1 years for HF patients without ID/A. The share of female patients was 58.5% for the group of HF patients with ID/A and 54.1% for the group of HF patients without ID/A. Female HF patients were on average older in both groups, but the difference was notably smaller in the group of HF patients with ID/A (women: 80.5 ± 11.0 years and men: 77.2 ± 10.5 years) than in the group of HF patients without ID/A (women: 79.3 ± 11.4 years and men: 73.6 ± 12.2 years).

Heart failure patients with ID/A presented with NYHA functional classes I (3%), II (13%), III (19%), and IV (20%). Most of the patients were classified as NYHA functional class N/A (45%) due to NYHA functional class unspecific ICD-10-GM diagnoses in the index quarter. In contrast, HF patients without ID/A presented with NYHA functional classes I (5%), II (15%), III (13%), IV (9%), and NYHA functional class N/A (58%).

Mortality

Heart failure patients with ID/A had a higher all-cause mortality (17.8% vs. 10.8%, χ^2 test $P < 0.01$) (*Figure 1*) in general, whereas for HF patients with NYHA functional class IV, all-cause mortality was higher in the group of HF patients without ID/A (36.4% vs. 34.7%, χ^2 test $P < 0.01$).

Figure 1 All-cause mortality stratified by NYHA functional classes.



Legend: HF=heart failure; NYHA=New York Heart Association; ID/A=iron deficiency/anemia; N/A=not applicable/available.

Iron treatment

The majority of HF patients with ID/A did not receive iron treatment (56.1%). Oral iron was administered in 37.9% and intravenous iron was administered in 6.0% of patients.

Health care utilization

The all-cause hospitalization rate for HF patients with ID/A was 72.9% in contrast to 50.5% (χ^2 test $P < 0.01$) for HF patients without ID/A. HF-related hospitalization occurred in 50.4% of the HF patients with ID/A and in 31.1% (χ^2 test $P < 0.01$) of the HF patients without ID/A. The average all-cause hospitalization lasted 14.6 days for HF patients with ID/A and 14.0 days (*t*-test $P < 0.01$) for HF patients without ID/A. The average length of stay per HF-related hospitalization was 15.4 days for HF patients with ID/A compared with 13.6 days (*t*-test $P < 0.01$) for HF patients without ID/A.

On average, HF patients with ID/A had 31.8 HF-related outpatient visits compared with 19.3 (*t*-test $P < 0.01$) in HF patients without ID/A. The most physician contacts were with a primary care physician (10.5 contacts), a nephrologist (6.1 contacts), or an internist working as primary care provider (3.9 contacts) for HF patients with ID/A. In the group of HF patients without ID/A, the most physician contacts were also with a primary care physician (7.8 contacts), an internist working as primary care provider (2.9 contacts), or a laboratory physician with 1.4 contacts, respectively.

Sick leave

A share of 5.3% of the HF patients without ID/A had at least one episode of sick leave during the study period. The proportion was 2.0% (χ^2 test $P < 0.01$) in the group of HF patients with ID/A. HF-related sick leave occurred in 0.7% of the HF patients without ID/A and in 0.3% (χ^2 test $P < 0.01$) of the HF patients with ID/A.

Health care costs

The mean annual overall health care costs of the surviving patients amounted to €14 998 for HF patients with ID/A and amounted to €6916 (*t*-test $P < 0.01$) for HF patients without ID/A. The cost driver in both groups was inpatient care. Mean annual overall health care costs of the deceasing HF patients were notably higher than those of the surviving HF patients. The main cost driver was also inpatient care. However, all other cost domains showed decreasing costs for the deceased HF patients (*Table 1*).

Matching analysis—incremental burden of iron deficiency anaemia

Matching heart failure patients without iron deficiency anaemia to heart failure patients with untreated incident iron deficiency anaemia

The exact matching using age, sex, and NYHA functional class resulted in 3048 HF patients without ID/A and 3048 HF patients with untreated incident ID/A. The standardized difference for baseline costs reached 3.5%, which is below the threshold of 10% as criteria for balanced comparison groups.

Demographics and New York Heart Association functional classes

The mean age of the matched cohorts of HF patients without ID/A and HF patients with untreated incident ID/A was 79.9 years (±10.1 years). More than half of the patients were women (58.1%). The proportion of the NYHA functional classes was NYHA I 2.9%, NYHA II 12.2%, NYHA III 20.1%, NYHA IV 20.1%, and NYHA N/A 44.6%.

Mortality

Heart failure patients with untreated incident ID/A had a significantly higher all-cause mortality than HF patients without ID/A (33.1% vs. 24.1%, McNemar test $P < 0.01$). This was observed overall individual NYHA functional classes except for NYHA I where the same trend did not reach statistical significance (*Table 2*). When stratified by male and female patients, the all-cause mortality rate was significantly higher for HF patients with untreated incident ID/A for the two NYHA functional classes III and IV for both sexes. Male patients had a higher all-cause mortality than their female counterparts in both groups. However, the highest all-cause mortality was observed in female HF patients with incident untreated ID/A and an NYHA functional class IV with 56.5% (*Table 2*).

The time-to-death analysis also revealed significant differences (log-rank test $P < 0.01$) between the two matched cohorts. *Figure 2* shows the Kaplan–Meier curves for the overall

Table 1 Annual mean health care costs per cost domain and in total—unmatched comparison

	HF patients with ID/A		HF patients without ID/A	
Cost domain/group	Survivor	Deceased	Survivor	Deceased
Inpatient care	€8463	€16 091	€3946	€12 088
Outpatient care	€3082	€1817	€1075	€721
Pharmaceuticals	€2862	€1717	€1512	€1224
Devices and aids	€534	€336	€270	€229
Sick leave payments	€58	€21	€113	€28
Total	€14 998	€19 983	€6916	€14 290

HF, heart failure; ID/A, iron deficiency/iron deficiency anaemia.

Table 2 All-cause mortality rates for HF patients without ID/A and for HF patients with untreated incident ID/A—1:1 matched comparison

	NYHA (max. in 2013)	HF without ID/A		HF with untreated incident ID/A without iron treatment		McNemar test
		n	%	*n*	%	*P*-value
Number of deceased patients—male	NYHA N/A	123	23.0	167	31.2	<0.01
	NYHA I	7	17.9	5	12.8	0.53
	NYHA II	19	10.9	46	26.3	<0.01
	NYHA III	71	26.6	105	39.3	<0.01
	NYHA IV	109	41.6	138	52.7	0.01
	NYHA I–IV	206	27.7	294	39.6	<0.01
	Total	329	25.7	461	36.1	<0.01
Number of deceased patients—female	NYHA N/A	142	17.2	169	20.5	0.07
	NYHA I	<5	8.0	7	14.0	0.32
	NYHA II	36	18.4	45	23.0	0.24
	NYHA III	66	19.0	128	36.9	<0.01
	NYHA IV	159	45.2	199	56.5	<0.01
	NYHA I–IV	265	28.0	379	40.1	<0.01
	Total	407	23.0	548	31.0	<0.01
Number of deceased patients—both	NYHA N/A	265	19.5	336	24.7	<0.01
	NYHA I	11	12.4	12	13.5	0.82
	NYHA II	55	14.8	91	24.5	<0.01
	NYHA III	137	22.3	233	37.9	<0.01
	NYHA IV	268	43.6	337	54.9	<0.01
	NYHA I–IV	471	27.9	673	39.9	<0.01
	Total	736	24.1	1.009	33.1	<0.01

HF, heart failure; ID/A, iron deficiency/iron deficiency anaemia; NYHA, New York Heart Association.

population of HF patients without ID/A and those with HF and untreated incident ID/A. The stratification by NYHA functional classes also showed significant differences between the two matched cohorts for all NYHA functional classes except for NYHA I (*Figure 2*).

Health care utilization

The analysis of health care utilization revealed significant differences in the rate of all-cause hospitalized patients (HF patients without ID/A: 82.6%, HF patients with untreated incident ID/A: 83.8%, McNemar test $P = 0.03$). The rate of HF-related hospitalized patients did not differ significantly between the two matched cohorts (HF patients without ID/A: 64.0%, HF patients with untreated incident ID/A: 63.0%, McNemar test $P = 0.17$). HF patients with untreated incident ID/A had significantly more all-cause hospitalizations (mean 2.2, Wilcoxon signed rank test $P < 0.01$) and similar HF-related hospitalizations (mean 1.2, Wilcoxon signed rank test $P = 1$) compared with HF without ID/A.

The average duration of an all-cause hospitalization was 30.8 days for HF patients without ID/A and 31.6 days for HF patients with untreated incident ID/A (Wilcoxon signed rank test $P = 0.04$). HF-related hospitalizations were of shorter duration in both groups (16.9 days for HF patients without ID/A and 17.8 days for HF patients with untreated incident ID/A) but significantly longer for HF patients with untreated incident ID/A (Wilcoxon signed rank test $P = 0.01$).

Health care costs

The analysis of annual all-cause health care costs revealed incremental costs of €849 for the HF patients with untreated incident ID/A (Wilcoxon signed rank test $P < 0.01$) compared with HF patients without ID/A. In detail, HF patients with untreated incident ID/A surviving the study period had €385 higher total mean annual health care costs than HF patients without ID/A (Wilcoxon signed rank test $P = 0.81$), whereas the total mean annual health care costs of deceased HF patients were higher in HF patients without ID/A (Wilcoxon signed rank test $P < 0.01$). The cost drivers were the costs for inpatient care in both comparison groups and for all subgroups (*Table 3*).

Matching analysis—comparison of treatment options for iron deficiency anaemia

Matching heart failure patients with iron deficiency anaemia receiving no iron treatment to heart failure patients with iron deficiency anaemia receiving oral iron treatment and to heart failure patients with iron deficiency anaemia receiving intravenous iron treatment

For the comparison of treatment options for ID/A, a total of 10 217 HF patients (5731 HF patients with ID/A receiving no iron treatment, 3870 HF patients with ID/A receiving oral iron treatment, and 616 HF patients with ID/A receiving intravenous iron treatment) were available in the database for the analysis. After the exclusion of dialysis-dependent patients, 5645 HF patients with ID/A receiving no iron treatment, 3837 HF patients with ID/A receiving oral iron treatment, and 394 HF patients with ID/A receiving intravenous iron treatment remained in the comparison groups.

Figure 2 Kaplan–Meier curves for HF patients without ID/A and for HF patients with untreated incident ID/A—overall and stratified by NYHA functional class. HF, heart failure; ID/A, iron deficiency anaemia; NYHA, New York Heart Association.

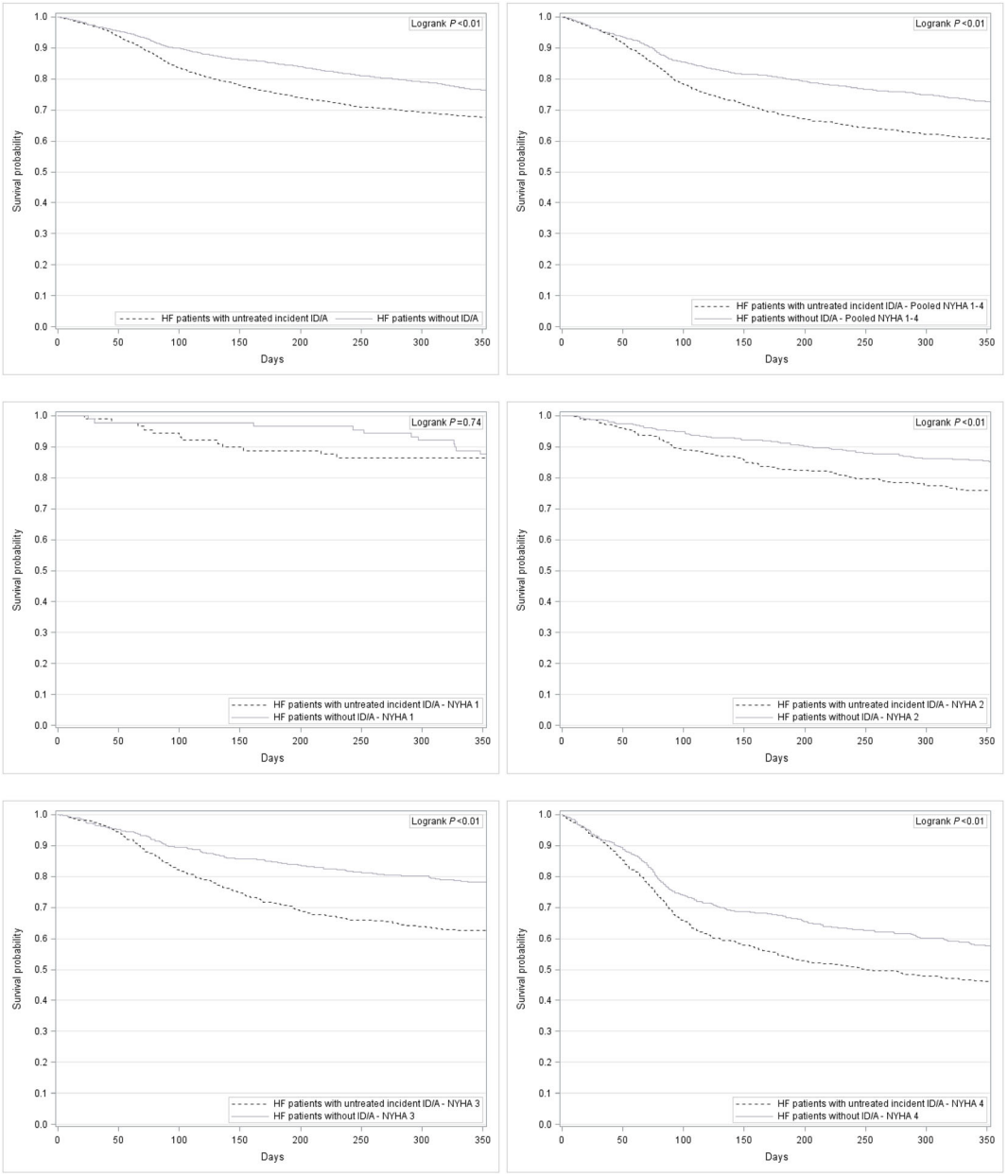


Table 3 Annual mean health care costs per cost domain and in total—1:1 matched comparison

	HF patients without ID/A			HF patients with untreated incident ID/A		
Cost domain/group	All patients	Survivor	Deceased	All patients	Survivor	Deceased
Inpatient care	€12 420	€10 245	€19 251	€13 833	€10 932	€19 696
Outpatient care	€1102	€1201	€790	€1063	€1258	€669
Pharmaceuticals	€2391	€2582	€1792	€1891	€2217	€1230
Devices and aids	€472	€543	€247	€496	€613	€258
Sick leave payments	€114	€140	€34	€65	€75	€44
Total	€16 498	€14 711	€22 113	€17 347	€15 096	€21 896

HF, heart failure; ID/A, iron deficiency/iron deficiency anaemia.

The exact match using age groups of 5 years, sex, and NYHA functional class resulted in 352 patients in each matched cohort. The groups were considered to be balanced with a standardized difference of 0% for sex and all NYHA functional classes. The standardized differences for exact age and baseline costs reached up to 1.4% and 4.92%, respectively, also indicating balanced matched cohorts.

Demographics and New York Heart Association classes

The majority of HF patients in the three matched cohorts was female with 58% of the population. The average age was 79.3 years (±8.7 years) for HF patients with ID/A receiving no iron treatment, 79.4 years (±8.6 years) for HF patients with ID/A receiving oral iron treatment, and 79.3 years (±8.5 years) for HF patients with ID/A receiving intravenous iron treatment. The proportion of NYHA functional classes was 1.4% NYHA I, 12.2% NYHA II, 16.8% NYHA III, 8.5% NYHA IV, and 61.1% NYHA N/A.

Mortality

A total of 23.6% of the HF patients with ID/A receiving no iron treatment deceased in the follow-up period. HF patients with ID/A receiving oral iron treatment had a lower all-cause mortality with 22.4%, and HF patients with ID/A receiving intravenous iron treatment had the lowest all-cause mortality with 18.5%. Men had a higher risk of dying compared with women in all three matched cohorts with 27.9% vs. 20.5% for HF patients with ID/A receiving no iron treatment, 24.5% vs. 21.0% for HF patients with ID/A receiving oral iron treatment, and 21.1% vs. 16.6% for HF patients with ID/A receiving intravenous iron treatment (*Table 4*).

The time-to-death analysis revealed a significant advantage for HF patients with ID/A receiving intravenous iron treatment compared with HF patients with ID/A receiving no iron treatment in NYHA functional class II (log-rank test $P = 0.01$), NYHA functional class III (log-rank test $P = 0.01$), and pooled NYHA functional classes I–IV (log-rank test $P < 0.01$), whereas oral iron treatment compared with no iron treatment only showed a significant advantage in NYHA functional class III (log-rank test $P = 0.02$).

Direct comparison of oral iron treatment and intravenous iron treatment favoured intravenous iron treatment in NYHA functional class II patients (log-rank test $P = 0.02$) and revealed the same trend for the pooled NYHA functional classes I–IV (log-rank test $P = 0.13$). See *Figure 3–5* for individual Kaplan–Meier curves for HF patients with ID/A stratified by treatment option and NYHA functional classes.

Health care utilization

Heart failure patients with ID/A receiving no iron treatment had the highest all-cause hospitalization rate (78.1%) of the three matched cohorts compared with 76.4% for HF patients with ID/A receiving oral iron treatment and 70.7% for HF patients with ID/A receiving intravenous iron treatment. No significant difference was observed between the HF patients with ID/A receiving no iron treatment and those receiving oral iron treatment (McNemar test $P = 0.32$). In contrast, the all-cause hospitalization rate of HF patients with ID/A receiving intravenous iron treatment differed significantly from those receiving no iron treatment (McNemar test $P < 0.01$) and those receiving oral iron treatment (McNemar test $P < 0.01$). More than half of the HF patients with ID/A receiving no iron treatment (53.7%) and of the HF patients with ID/A receiving oral iron treatment (51.4%) experienced HF-related hospitalizations. HF patients with ID/A receiving intravenous iron treatment had a lower HF-related hospitalization rate with 48.6% (χ^2 test $P < 0.01$). HF-related hospitalization rates increased with higher NYHA functional class from 31.2%–38.1% for NYHA functional class N/A up to 90.0%–93.3% for NYHA functional class IV.

Heart failure patients with ID/A receiving no iron treatment had on average 2.0 all-cause hospitalizations and 0.9 HF-related hospitalizations. HF patients with ID/A receiving oral or intravenous iron treatment had similar average hospitalizations (2.0 and 1.9 all-cause hospitalizations; 0.9 and 0.9 HF-related hospitalizations, respectively). The average duration of an all-cause hospitalization was 30.1 days for HF patients with ID/A receiving no iron treatment, 26.6 days for HF patients with ID/A receiving oral iron treatment, and 24.9 days for HF patients with ID/A receiving intravenous iron treatment. HF-related hospitalizations were of shorter duration in all three matched cohorts (14.0 days for HF patients with ID/A receiving no iron treatment, 13.0 days for HF patients with ID/A receiving oral iron treatment, and 12.0 days for HF patients with ID/A receiving intravenous iron treatment).

The main contact in the outpatient setting for HF patients with ID/A was the primary care physician with 13.5 visits for HF patients with ID/A receiving no iron treatment, 13.4 visits for HF patients with ID/A receiving oral iron treatment, and 13.9 visits for HF patients with ID/A receiving intravenous iron treatment. The second most contact was with an internist working as a primary care provider with 3.7, 4.7, and 5.9 visits, respectively. In contrast, a cardiologist was only seen 0.7, 0.9, and 1.4 times by the respective HF patient groups. All-cause sick leave occurred in the group of HF patients with ID/A receiving no iron treatment with 2.6% of the HF patients having sick leave and in less than 1.4% for HF patients with ID/A receiving oral treatment and for HF patients with ID/A receiving intravenous iron treatment (less than five patients). The average length of sick leave in of HF patients with ID/A receiving no iron treatment was 2.3 days.

Health care costs

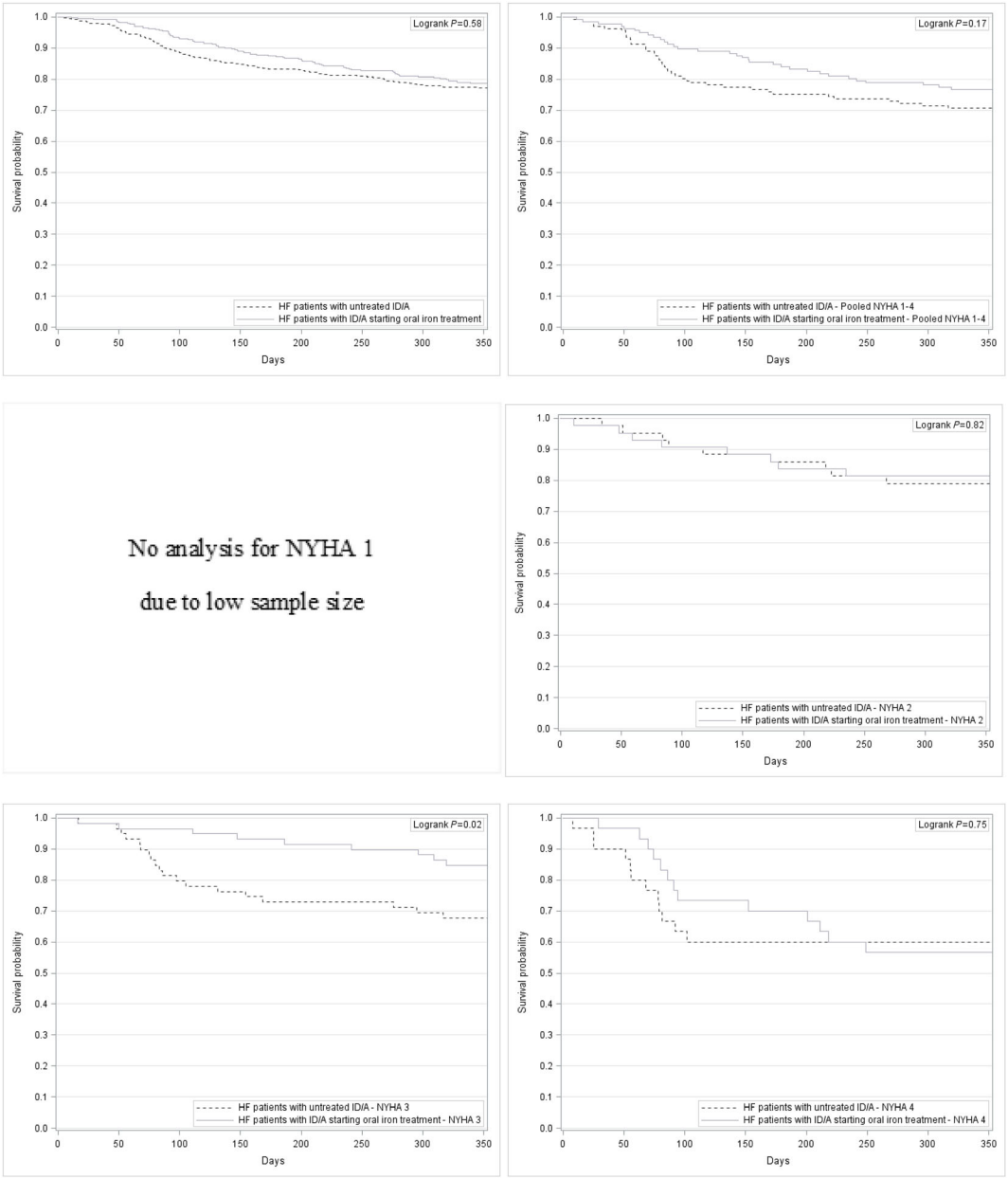
The comparison of all-cause annual health care costs identified HF patients with ID/A receiving no iron treatment to have the highest mean costs (€15 144). The lowest all-cause annual costs were observed in HF patients with ID/A receiving oral iron treatment (€14 130). The cost driver in all three

Table 4 All-cause mortality rates for HF patients with ID/A stratified by treatment option—1:1:1 matched comparison

	NYHA functional class	HF patients with ID/A receiving no iron treatment		HF patients with ID/A receiving oral iron treatment		HF patients with ID/A receiving intravenous iron treatment		No treatment vs. oral treatment	No treatment vs. intravenous treatment	Oral treatment vs. intravenous treatment
								McNemar test	McNemar test	McNemar test
		n	%	*n*	%	*n*	%	*P*-value	*P*-value	*P*-value
Number of deceased patients—male	NYHA N/A	19	22.6	23	27.4	21	25.0	0.43	0.71	0.72
	NYHA I	—	—	—	—	—	—	—	—	—
	NYHA II	6	28.6	—	—	—	—	—	—	—
	NYHA III	9	36.0	—	—	5	20.0	—	0.21	—
	NYHA IV	7	46.7	5	33.3	5	33.3	0.41	0.48	1.00
	NYHA I–IV	22	34.9	13	20.6	10	15.9	0.06	0.01	0.47
	Total	41	27.9	36	24.5	31	21.1	0.48	0.17	0.48
Number of deceased patients—female	NYHA N/A	21	16.0	22	16.8	20	15.3	0.86	0.85	0.73
	NYHA I	—	—	—	—	—	—	—	—	—
	NYHA II	—	—	5	22.7	—	—	—	—	—
	NYHA III	11	32.4	6	17.6	—	—	0.17	—	—
	NYHA IV	6	40.0	8	53.3	8	53.3	0.48	0.32	1.00
	NYHA I–IV	21	28.4	21	28.4	14	18.9	1.00	0.13	0.11
	Total	42	20.5	43	21.0	34	16.6	0.90	0.25	0.22
Number of deceased patients—both	NYHA N/A	40	18.6	45	20.9	41	19.1	0.51	0.89	0.62
	NYHA I	—	—	—	—	—	—	—	—	—
	NYHA II	10	23.3	9	20.9	—	—	0.76	—	—
	NYHA III	20	33.9	10	16.9	9	15.3	0.04	0.02	0.78
	NYHA IV	13	43.3	13	43.3	13	43.3	1.00	1.00	1.00
	NYHA I–IV	43	31.4	34	24.8	24	17.5	0.21	0.00	0.10
	Total	83	23.6	79	22.4	65	18.5	0.70	0.07	0.17

HF, heart failure; ID/A, iron deficiency/iron deficiency anaemia; NYHA, New York Heart Association.

Figure 3 Kaplan–Meier curves for HF patients with untreated ID/A and for HF patients with ID/A starting oral iron treatment—overall and stratified by NYHA functional class. HF, heart failure; ID/A, iron deficiency anaemia; NYHA, New York Heart Association.

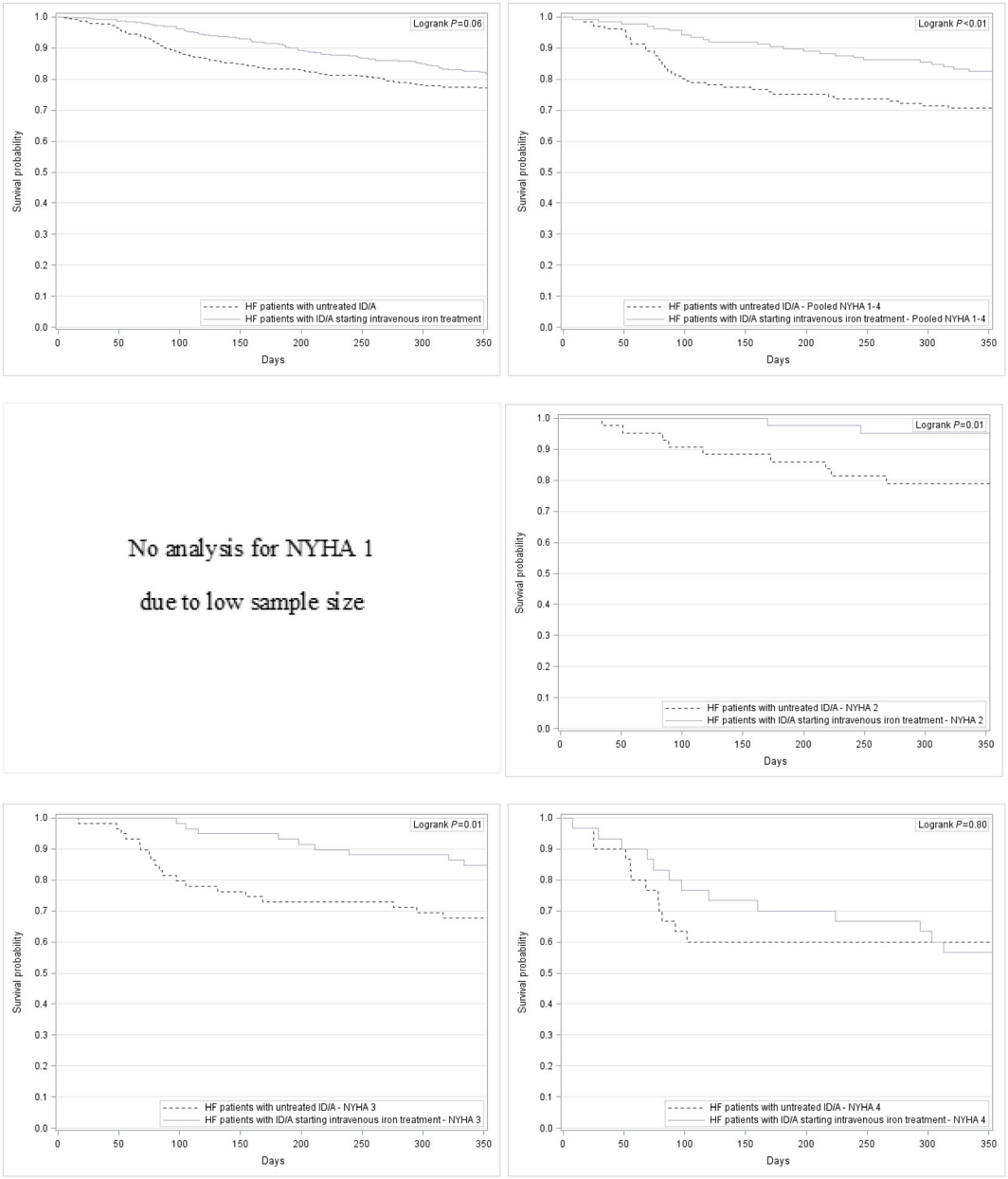


matched cohorts was costs for inpatient care, accounting for 74.3% in HF patients with ID/A receiving no iron treatment, 71.3% in HF patients with ID/A receiving oral iron treatment, and 51.7% in HF patients with ID/A receiving intravenous iron treatment. The smaller share of costs for inpatient care in the intravenous iron group was compensated by a share of 33.9% of total costs for pharmaceuticals, which accounted in contrast for 14.5% in HF patients with ID/A receiving no iron treatment and for 16.2% in HF patients with ID/A receiving oral iron treatment. Deceased HF patients had 1.3, 1.3, and 1.4 times higher annual mean total health care costs (*Table 5*).

Brief summary of main results

This study estimated the current prevalence of HF in Germany to be 4537.4 per 100 000 with a share of 11.1% also suffering from ID/A. HF was shown to be a disease of the

Figure 4 Kaplan–Meier curves for HF patients with untreated ID/A and for HF patients with ID/A starting intravenous iron treatment—overall and stratified by NYHA functional class. HF, heart failure; ID/A, iron deficiency anaemia; NYHA, New York Heart Association.

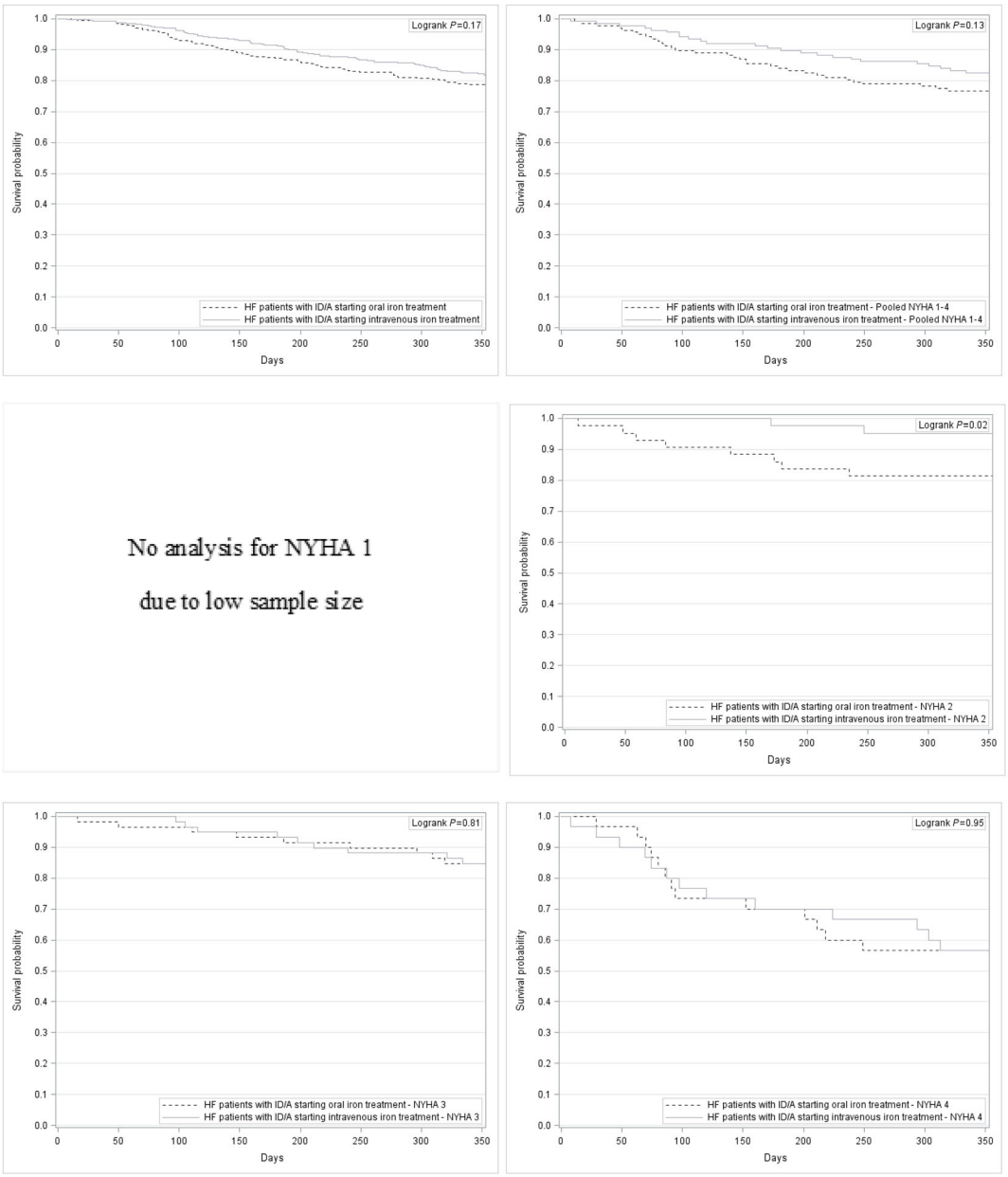


elderly (mean age 77.0 ± 12.0 years). Most HF patients with ID/A did not receive iron treatment (56.1%).

Heart failure patients with untreated incident ID/A suffered from a significantly higher all-cause mortality than matched HF patients without ID/A (33.1% vs. 24.1%, McNemar test $P < 0.01$), independently of NYHA functional class. The incremental health care costs of untreated incident ID/A were estimated at €849 with inpatient care being the cost driver.

The comparison of treatment options for ID/A revealed the highest all-cause mortality for HF patients with untreated ID/A (23.6%), whereas patients receiving intravenous iron treatment had the lowest all-cause mortality of 18.5% (McNemar test $P = 0.07$). A significant survival benefit was shown for the NYHA functional classes II (log-rank test $P = 0.01$) and III (log-rank test $P = 0.01$) as well as for the pooled NYHA functional classes I–IV (log-rank test $P < 0.01$). For oral iron treatment, a significant survival benefit compared with no iron treatment was only shown for NYHA functional class III (log-rank test $P = 0.02$). Total annual health care costs ranged from €14 130 for HF patients with

Figure 5 Kaplan–Meier curves for HF patients with ID/A starting oral iron treatment and for HF patients with ID/A starting intravenous iron treatment —overall and stratified by NYHA functional class. HF, heart failure; ID/A, iron deficiency anaemia; NYHA, New York Heart Association.



ID/A receiving oral iron treatment to €15 144 for HF patients with ID/A receiving no iron treatment. The costs for inpatient care were the cost driver in all three cohorts.

Discussion

General results for prevalence and demographics

This study provides current data on the prevalence of HF in Germany (4537.4 per 100 000 individuals). Compared with DEGAM[3] and Störk *et al.*[4] (3956.3 per 100 000), our study shows that the prevalence of HF has significantly increased over the last years. It shows that about 11.1% of all HF patients are diagnosed with ID/A and that more than half of these HF patients (56.1%) receive no ID/A specific treatment. The proportion of HF patients diagnosed with ID/A is significantly lower than what is known from the literature with up to 50%. Moreover, the share of ID alone among HF patients was 32.5% as reported by Klip *et al*. whereas in our study, this proportion only reached 0.9%.[11] This might be related to the findings from Wienbergen *et al*.,[23] who reported that iron status is often not determined (37.8%)

Table 5 Annual mean health care costs per cost domain and in total—1:1:1 matched comparison

	HF patients with ID/A receiving no iron treatment			HF patients with ID/A receiving oral iron treatment			HF patients with ID/A receiving intravenous iron treatment		
Cost domain/group	All patients	Survivor	Deceased	All patients	Survivor	Deceased	All patients	Survivor	Deceased
Inpatient care	€11 249	€9734	€16 160	€10 078	€8724	€14 758	€7806	€6686	€12 753
Outpatient care	€1149	€1253	€811	€1178	€1278	€830	€1558	€1636	€1214
Pharmaceuticals	€2193	€2485	€1247	€2288	€2564	€1334	€5114	€5242	€4548
Devices and aids	€511	€562	€346	€561	€607	€400	€553	€538	€617
Sick leave payments	€42	€55	€0	€25	€32	€0	€54	€67	€0
Total	€15 144	€14 089	€18 564	€14 130	€13 206	€17 321	€15 085	€14 169	€19 131

HF, heart failure; ID/A, iron deficiency/iron deficiency anaemia.

despite of European Society of Cardiology (ESC) guideline 2016 recommendation.[1]

Comparison results for heart failure patients without iron deficiency anaemia vs. heart failure patients with untreated incident iron deficiency anaemia

This study revealed that HF patients with untreated incident ID/A had a lower 1 year survival probability than HF patients without ID/A, irrespective of NYHA class. Similar implications are found in the literature that highlights the need to diagnose and treat ID/A among HF patients.[9,12,24] Anker *et al.*[13] and Ponikowski *et al.*[14] showed that treating HF patients with ID/A with intravenous iron supplement (ferric carboxymaltose) improves symptoms, functional capacity, and quality of life. For patients with systolic HF and ID receiving intravenous iron supplement treatment also a reduction of recurrent CV and HF-related hospitalizations and all-cause and CV mortality was reported.[15] From a cost perspective, the cost driver for the treatment of HF with and without ID/A is the inpatient costs. This was also shown by a review of Lesyuk *et al.* who identified 16 cost-of-illness studies from Germany, Greece, Ireland, Italy, Nigeria, Poland, South Korea, Spain, Sweden, and the USA. Most of the included studies found hospital admission to be the most expensive part of the total costs for HF patients. Total annual costs per HF patient were estimated lowest for South Korea with $868 and highest for Germany with $25 532.[25] Out of the 16 studies, two studies reported annual costs for Germany. Zugck *et al.* reported annual costs ranging from €11 794 to €16 303 for 2002 that is similar to our findings of €16 498 for HF patients without ID/A and €17 347 for HF patients with untreated incident ID/A.[26] Neumann *et al.* reported direct medical costs of €2879 for all HF patients in Germany in 2006.[27] These costs are not comparable with our results as they refer to medical costs directly linked to HF treatment whereas our cost estimates include all health care expenditures of HF patients, as the focus of our study was to investigate the impact of ID/A in HF.

Comparison results for heart failure patients with iron deficiency anaemia and no evidence of iron treatment to heart failure patients with iron deficiency anaemia and oral iron treatment and to heart failure patients with iron deficiency anaemia and intravenous iron treatment

Heart failure patients with ID/A and no iron medication have the highest mortality rate in all study cohorts. HF patients with ID/A are mainly treated by a primary care physician and see a cardiologist on irregularly basis.

Recent studies have shown that treatment with intravenous iron can improve the functional capacity, symptoms, and quality of life in patients with HF and ID.[13,14,28,29] The use of oral iron failed to improve exercise capacity as was shown by Lewis *et al.*[30]

This study revealed that HF patients with untreated incident ID/A had a lower 1 year survival probability than HF patients without ID/A, irrespective of NYHA class. Additionally, the study showed that iron treatment is associated with an improved survival probability. This trend was particularly evident in HF patients with ID/A starting intravenous iron treatment. They had a significantly higher 1 year survival probability than untreated patients in most NYHA classes. Intravenous iron treatment was also associated with survival advantages when compared with oral iron treatment, especially among NYHA class II patients.

Internal validity and risk of bias

Between 45% and 61% of the HF patients in this study were classified as NYHA functional class N/A, meaning that they had no NYHA functional class specific ICD-10-GM code in the index quarter, but an ICD-10-GM diagnosis of I50, I50.0, I50.00, I50.01, I50.1, I50.19, and I50.9. An alternative algorithm or a more NYHA functional class specific coding practice might provide the opportunity to group these patients also into the four NYHA functional classes and thereby would enhance the statistical power of the results. Otherwise, it could also influence the results in the opposite direction.

German claims data contain no direct information about the reason of death. The present study therefore analysed the overall mortality of HF patients. Nevertheless, the data source provides sufficient information to analyse the overall mortality and the time to death as German claims data contain information on the status of an individual whether it is alive or dead and the corresponding insurance time. Moreover, the information recorded in the inpatient setting contains a reason for discharge from hospital that could be death and in combination with the end date of the inpatient stay provides the exact date of death. However, more disease specific information would be desirable to analyse disease specific mortality rates.

Strengths and weaknesses

This study has some weaknesses. First, German claims data contain no clinical information that is not necessary for the reimbursement purpose of the data collection. Therefore, the study had to rely on the information that is coded in the utilized coding systems namely the ICD-10-GM catalog. The ICD-10-GM catalog provides information about the NYHA functional classes I to IV but contains also non-NYHA functional class specific codes. In cases where only these codes were recorded, no further clinical information was available to classify these HF patients into one of the NYHA functional groups.

Furthermore, the data source contains no information on the intention of the treating physicians. For a proportion of the 56.1% HF patients with ID/A, who received no iron treatment, the decision of not treating these patients with iron medication might have been an active and reasonable decision of the treating physician. Laboratory data to verify this assumption are not available in German claims data, but the degree of ID/A is supposed to have an impact on the treatment decision of the attending physician.

This study has some major strengths. First, the utilized data source allows to generalize the results of this study to a major part of the German population as approximately 85% of the German population are covered by the SHI. In contrast to registries and clinical trials where a selected population is investigated, this analysis might not be affected by a selection bias. Second, participants of the German SHI system benefit on nearly full coverage of all health care services. Only little copayments exist in the German SHI and these are furthermore limited to 2% of the annual income of the insured individuals (1% for chronically ill individuals) §62 SGB V. German claims data therefore provide not only the full picture of costs from the payer's perspective but also nearly the full picture of all direct health care costs and the corresponding health care utilization.

Generalizability

The InGef research database is based on claims data from the SHI system but is adjusted to the German overall population in terms of age and sex. This fact limits the generalizability of the result for the overall SHI population as the proportion of women is higher in this population than in the overall German population due to the fact that proportionately, more men choose a private health insurance in Germany. On the other hand, the generalizability of the results to the German population might be biased due to the fact that individuals with an annual income above a defined threshold (so called 'Jahresarbeitsentgeltgrenze') could choose a private health insurance instead of the SHI. These individuals tend to be healthier than the individuals that have to be insured by the SHI.[31] Moreover, the prevalence of CV disease, for example, HF, shows regional differences among the federal states in Germany. The adjusted age and sex distribution of the InGef research database does not account for these regional differences.[5]

Limitations

In general, claims data analyses are subject to limitations, as they are primarily collected for accounting purposes, and therefore, clinical parameters are not covered. Furthermore, diagnoses in the outpatient setting are only recorded on a quarterly basis, which leads to an overestimation of HF-related outpatient visits in this analysis as all visits within a quarter were considered as HF related if an HF diagnosis was recorded in that quarter. Another limitation of the study is due to the fact, that 'over-the-counter' (OTC) medication is not recorded in the database. The group of HF patients with ID/A and no iron treatment might be overestimated if patients buy OTC iron treatment on their own. From an analytical standpoint, our analysis therefore shows conservative results for this patient group as some of these patients might benefit from OTC iron treatment that was not captured in the comparison.

Conclusions

Heart failure is associated with a major burden for patients and the health care system in terms of health care resource utilization, costs, and mortality. ID/A is an independent predictor of unfavourable outcome, and a cost driver in HF patients and HF patients with ID/A has higher all-cause mortality and causes higher health care utilization and costs. Compared with previous findings,[9,32] this claims database analysis suggests that ID/A is underdiagnosed in the German setting, which was also suggested elsewhere.[23,33] Especially ID alone is almost non-existent according to our findings.

The present study revealed that HF patients with ID/A are, on average, older and sicker in terms of NYHA classification, with a higher proportion of women than HF patients without ID/A. These findings are in line with evidence obtained in other observational studies.[9,12] In addition, the data suggest that ID/A in HF patients is undertreated and that intravenous iron is a rarely chosen treatment option in the German setting, despite clinical guidelines suggesting this treatment.[1] The total health care costs of HF patients increase with the presence of ID/A. HF patients with ID/A receiving pharmaceutical treatment with iron medication present with lower inpatient costs compared with HF patients with untreated ID/A. The additional costs for iron medication are still compensated by lower costs for inpatient care.

Our findings suggest that there is an unmet need for treating more HF patients with ID/A with iron medication, resulting in costs savings for the SHI and reduced mortality for the affected HF patients. However, more research is needed to evaluate long-time effects and to further investigate the cohort of undefined NYHA functional class.

Role of data owner

The data analysis was performed in cooperation between Xcenda GmbH and Elsevier Health Analytics.

Conflict of interest

I.B. and T.H. are employees of Vifor Pharma and Vifor Fresenius Medical Care Renal Pharma, Munich, Germany. The authors declare that no further conflict of interest exists.

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Modul 7

Burden of HPV related anogenital diseases in young women in Germany – An analysis of German statutory health insurance claims data from 2012 to 2017

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Burden of HPV related anogenital diseases in young women in Germany – an analysis of German statutory health insurance claims data from 2012 to 2017

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Abstract

Background: Most individuals are infected with human papillomavirus (HPV) at least once in their lifetime. Infections with low-risk types can cause genital warts, whereas high-risk types can cause malignant tumors. The aim of this study was to determine the burden of anogenital diseases potentially related to HPV in young women based on German statutory health insurance claims data.

Methods: We conducted a retrospective claims data analysis using the "Institute for Applied Health Research Berlin" (InGef) Research Database, containing claims data from approximately 4 million individuals. In the period from 2012 to 2017 all women born in1989–1992, who were continuously insured between the age of 23–25 years were identified. Using ICD-10-GM codes (verified diagnosis in the outpatient sector or primary or secondary diagnosis in the inpatient sector) the administrative prevalence (95% confidence interval) of genital warts (A63.0), anogenital diseases grade I (K62.8, N87.0, N89.0, N90.0), grade II (N87.1, N89.1, N90.1) and grade III (D01.3, D06.-, D06.0, D07.1, D07.2, N87.2, N89.2, N90.2) was calculated (women with diagnosis divided by all women).

Results: From 2012 to 2017, a total of 15,358 (birth cohort 1989), 16,027 (birth cohort 1990), 14,748 (birth cohort 1991) and 14,862 (birth cohort 1992) women at the age of 23–25 were identified. A decrease of the administrative prevalence was observed in genital warts (1.30% (1.12–1.49) birth cohort 1989 vs. 0.94% (0.79–1.10) birth cohort 1992) and anogenital diseases grade III (1.09% (0.93–1.26) birth cohort 1989 vs. 0.71% (0.58–0.86) birth cohort 1992). In anogenital diseases grade III, this trend was especially observed for severe cervical dysplasia (N87.2) (0.91% (0.76–1.07) birth cohort 1989 vs. 0.60% (0.48–0.74) birth cohort 1992). In contrast, anogenital diseases grade I (1.41% (1.23–1.61) birth cohort 1989 vs. 1.31% (1.14–1.51) birth cohort 1992) and grade II (0.61% (0.49–0.75) birth cohort 1989 vs. 0.52% (0.42–0.65) birth cohort 1992) remained stable.

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(Continued from previous page)
Conclusions: A decrease of the burden of anogenital disease potentially related to HPV was observed in the younger birth cohorts. This was observed especially for genital warts and anogenital diseases grade III. Further research to investigate this trend for the upcoming years in light of varying HPV vaccination coverage for newer birth cohorts is necessary.

Keywords: Human papillomavirus (HPV), Genital warts, Cervical intraepithelial neoplasia, Prevalence, Claims data, Statutory health insurance, Germany

Background

Human papillomavirus (HPV) infection belongs to the most frequent sexually transmitted infections in men and women worldwide [1]. Nearly all sexually active individuals will acquire at least one HPV infection in their life [2]. Although the majority of HPV infections are cleared spontaneously within a couple of months, they may become persistent with a subsequently increased risk of developing genital warts and certain cancer types [3].

HPV types capable of infecting mucosal epithelia are subdivided into low-risk and high-risk types. The low-risk types can lead to anogenital warts (condylomata acuminata). Low-risk types HPV 6 and 11 are responsible for approximately 90% of all anogenital wart cases [4]. Worldwide, several million cases of anogenital warts occur each year in both sexes, with a peak incidence between 20 and 24 years of age for women and between 25 and 29 years among men [5]. In Germany, a crude incidence rate of anogenital warts for women aged 10 to 79 years old was reported with 181 per 100,000 person years in 2010 [6].

High-risk HPV types can cause malignant conditions such as cervical intraepithelial neoplasia and cervical cancer [7]. Additionally, precancerous lesions and cancers at other anogenital sites are known to be associated with high-risk HPV. In Germany, about 4600 women are newly diagnosed with cervical cancer every year and approximately 1500 women die from cervical cancer per year [8]. It is assumed that high-risk HPV infections cause almost all cervical cancers and precancers, approximately 90% of high-grade anal, vulvar and vaginal intraepithelial neoplasias, and approximately 30, 70, and 90% of vulvar, vaginal and anal cancers, respectively [9, 10]. There are at least 12 high-risk HPV types, of which HPV 16 and 18 are responsible for 45% of cervical high-grade intraepithelial neoplasia and 70% of cervical cancers. Approximately 70–90% of HPV associated precancers and cancers at non-cervical anogenital sites are induced by HPV 16 and 18 [9].

HPV vaccination can prevent certain HPV infections and HPV-related anogenital diseases. The European Medicines Agency (EMA) authorized the first HPV vaccines in 2006 (quadrivalent vaccine against HPV 6, 11, 16 and 18) and 2007 (bivalent HPV 16 and 18) [11]. The quadrivalent vaccine may protect against HPV types causing approximately 70% of cervical cancers and 90% of genital warts [3]. Since 2016, a 9-valent vaccine is available in Germany which in addition to HPV types 6, 11, 16, and 18 also immunizes against the high-risk HPV types 31, 33, 45, 52, and 58 [12, 13]. These five additional HPV types are supposed to account for 15–20% of all cervical carcinomas [14].

In Germany, the Standing Committee on Vaccination (STIKO) at the Robert Koch Institute (RKI) is responsible for recommendations on vaccinations. These are then covered by the statutory health insurance (SHI) for all insured persons according to the recommended conditions e.g. in terms of age and gender [15]. School-based or community-based vaccination programs do not exist in Germany. In 2007, the STIKO released the first recommendation for HPV vaccination of girls in the age group of 12–17 [16]. In August 2014, the STIKO lowered the recommended vaccination age to 9–14 years. Since then, only two doses have been recommended. For catch-up vaccinations at the age of 15–17 years, the STIKO continued to recommend three doses. Since 2018, HPV vaccination is recommended for girls and boys at the age of 9–14 with catch-up until the age of 17 [17]. In the first year after the introduction of the HPV vaccination in Germany (2008), the vaccination rate was reported with 32.2% for at least one dose in the target age group of the first STIKO recommendation (12- to 17-year-old girls) [18, 19]. In 2015, the HPV vaccination rate was 31.3% in 15 year old and 44.6% in 17 year old girls (3 doses) [20]. Thus, in comparison to other countries with vaccination programs in schools, Germany has a lower immunization coverage for HPV [21]. To date, the burden of HPV related anogenital diseases has not been systematically evaluated for female birth cohorts eligible to receive the HPV vaccine after its introduction in 2007 in Germany.

The aim of this study was to assess the burden of anogenital diseases potentially related to HPV in women at the age of 23–25 based on diagnoses documented in German sickness fund data. The burden of HPV-related anogenital diseases is poorly explored in the birth cohorts who had a chance to receive HPV vaccination directly after its introduction in Germany in 2007. By

assessing the first three birth cohorts (1990–1992) who were fully eligible for HPV vaccination according to the first STIKO recommendation and birth cohort 1989 which was partially eligible (this cohort turned 18 in 2007) we aimed to generate insights into the burden of potentially HPV-related anogenital diseases in these specific birth cohorts after the introduction of the HPV vaccination in Germany. HPV vaccination status of the study population could not be evaluated.

Methods

Data source

A retrospective claims database analysis was conducted using the "Institute for Applied Health Research Berlin" (InGef) Research Database. The database comprises anonymized healthcare claims data from approximately 8 million covered lives from about 60 different sickness funds. The data include patient demographics and characteristics, inpatient and outpatient diagnoses, surgeries and diagnostic codes, the healthcare resource utilization and costs of services for the inpatient care, outpatient care, pharmacological therapy, remedies, devices and aids, and sick leave in an anonymized case-by-case individual format. For scientific research projects, an adjusted analysis sample of the InGef database has been created which includes approximately 4 million covered lives structured to represent the German population in terms of age and gender according to the Federal Office of Statistics. The InGef sample represents about 5.5% of the German SHI population, whereas about 85% of the German population is insured by the SHI. It has been proven to have good external validity to the German population in terms of morbidity, mortality and drug use [22].

Study population

The STIKO recommendation for HPV vaccination from 2007 included girls between 12 and 17 years. Birth cohort 1989 turned 18 in 2007 and therefore, parts of the birth cohort were too old for the HPV vaccination according to the STIKO recommendation from 2007. The female birth cohorts 1990 to 1992 were the first female birth cohorts that fulfilled the recommended age criteria for HPV vaccination according to the STIKO. Thus, this study included the first three female birth cohorts (1990, 1991, and 1992) which were fully eligible to receive HPV vaccination according to the age recommended by STIKO in 2007 and furthermore, the birth cohort 1989 which was partially eligible to receive HPV vaccination according to the STIKO recommendation. In total, the study population comprised all women in the InGef Research Database from 2012 to 2017 who were born in 1989, 1990, 1991, or 1992. All women had to be continuously observable from the age of 23 to 25, except for women who deceased. Age was determined at December 31st of each year.

HPV related Anogenital diseases

The identification of potentially HPV-related anogenital diseases was based on International Statistical Classification of Diseases, German Modification (ICD-10-GM) codes. All potentially HPV-related anogenital diseases (cytologically or histologically derived) in the outpatient sector (verified diagnoses) and in the inpatient sector (main and secondary diagnoses) were identified (Table 1).

Administrative prevalence rates (APR)

The 3-year APR were calculated by dividing the total number of women in the respective birth cohort with the documentation of at least one of the defined ICD-10-GM codes by the total number of women in the respective birth cohort who were continuously observable in the observation period. The 3-year APR were reported in percent.

The 1-year APR for each age group in each female birth cohort and ICD-10-GM code group were calculated by using a similar formula: total number of women in the respective birth cohort and age group with at least one of the defined ICD-10-GM codes divided by the total number of women in the respective birth cohort and age group who were continuously observable in the

Table 1 List of ICD-10-GM codes utilized for identification of potentially HPV-related anogenital diseases

Group	Description	ICD-10-GM Code
Genital warts	Anogenital (venereal) warts (condylomata)	A63.0
Grade I	Other specified diseases of anus and rectum (AIN I & II)	K62.8
	Mild cervical dysplasia (CIN I)	N87.0
	Mild vaginal dysplasia (VAIN I)	N89.0
	Mild vulvar dysplasia (VIN I)	N90.0
Grade II	Moderate cervical dysplasia (CIN II)	N87.1
	Moderate vaginal dysplasia (VAIN II)	N89.1
	Moderate vulvar dysplasia (VIN II)	N90.1
Grade III	Carcinoma in situ of anus and anal canal (AIN III)	D01.3
	Carcinoma in situ of cervix uteri (CIN III)	D06.-
	Carcinoma in situ of endocervix	D06.0
	Carcinoma in situ of vulva (VIN III)	D07.1
	Carcinoma in situ of vagina (VAIN III)	D07.2
	Severe cervical dysplasia	N87.2
	Severe vaginal dysplasia, other	N89.2
	Severe vulvar dysplasia, other	N90.2
Carcinoma	Malignant neoplasm of cervix uteri	C53.-
	Malignant neoplasm of anus and anal canal	C21.-
	Malignant neoplasm of vulva	C51.-
	Malignant neoplasm of vagina	C52.-

respective calendar year. The 1-year APR were also reported in percent.

Furthermore, confidence intervals with 95% confidence level were calculated for the APR by applying the exact Clopper–Pearson method, which is based on the exact binomial distribution and not a large sample normal approximation and is rather suitable in case of a small n [23].

Results

The InGef Research Database included a total of 2,405,802 women from January 1st, 2012 to December 31st, 2017. In total, 15,358 (birth cohort 1989), 16,027 (birth cohort 1990), 14,748 (birth cohort 1991) and 14,862 (birth cohort 1992) women were continuously insured at the age of 23 to 25, also including women who deceased in this age period. Within the 3 years of observation a minimum of five (birth cohort 1990) and a maximum of 10 (birth cohort 1992) women deceased in the age period from 23 to 25 years (Fig. 1).

The highest 3-year administrative APR in all birth cohorts was observed for anogenital diseases grade I (1.41% in birth cohort 1989; 1.31% in birth cohort 1992), followed by genital warts (1.30% in birth cohort 1989; 0.94% in birth cohort 1992) and anogenital diseases grade III (1.09% in birth cohort 1989, 0.71% in birth cohort 1992). Anogenital diseases grade II (0.61% in birth cohort 1989, 0.52% in birth cohort 1992) and especially invasive carcinoma (0.12% in birth cohort 1989, 0.06% in birth cohort 1992) were less frequently documented (Fig. 2).

Genital warts

The highest 3-year APR for genital warts was observed for birth cohort 1989 with 1.30% (1.12–1.49). A lower 3-year APR was observed for the younger cohorts (0.94% (0.79–1.10) birth cohort 1992) (all birth cohorts in Fig. 2). The 1-year APR for genital warts is summarized for individual age years in the supplement (see ADDITIONAL FILE 1, Supplementary Figure 1).

Anogenital diseases grade I

Three-year APR trend for anogenital diseases grade I remained stable (1.41% (1.23–1.61) in birth cohort 1989 to 1.31% (1.14–1.51) in birth cohort 1992). A peak was observed in birth cohort 1990 (1.60% (1.41–1.80). Among the anogenital diseases grade I, mild cervical dysplasia (CIN I) was most frequently recorded, followed by other specified diseases of anus and rectum (AIN I & II). With a 3-year APR of a maximum of 0.12% for mild vaginal dysplasia (VAIN I) and 0.05% for mild vulvar dysplasia (VIN I) these two anogenital diseases were less frequently recorded compared with CIN I and AIN I & II (Fig. 3). 1-year APR for grade I disease are summarized for individual age years in the ADDITIONAL FILE 1, Supplementary Figure 2.

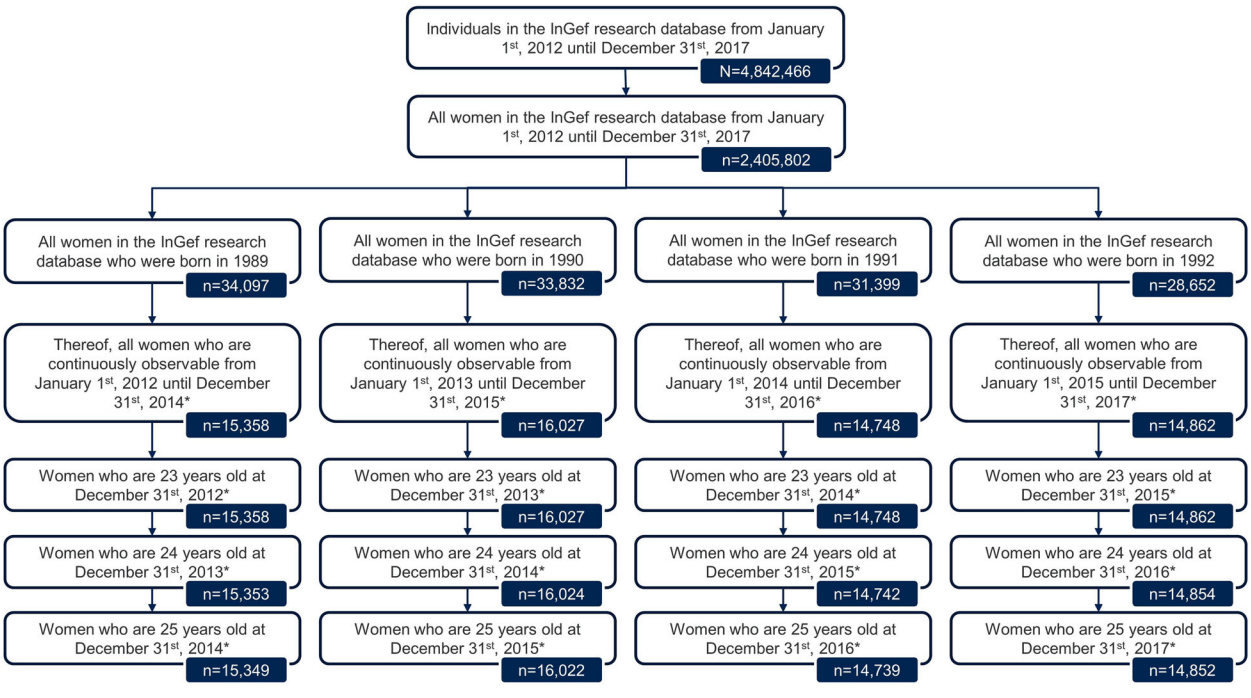

Fig. 1 Patient flowchart. * Including patients who deceased in the respective observation period/year

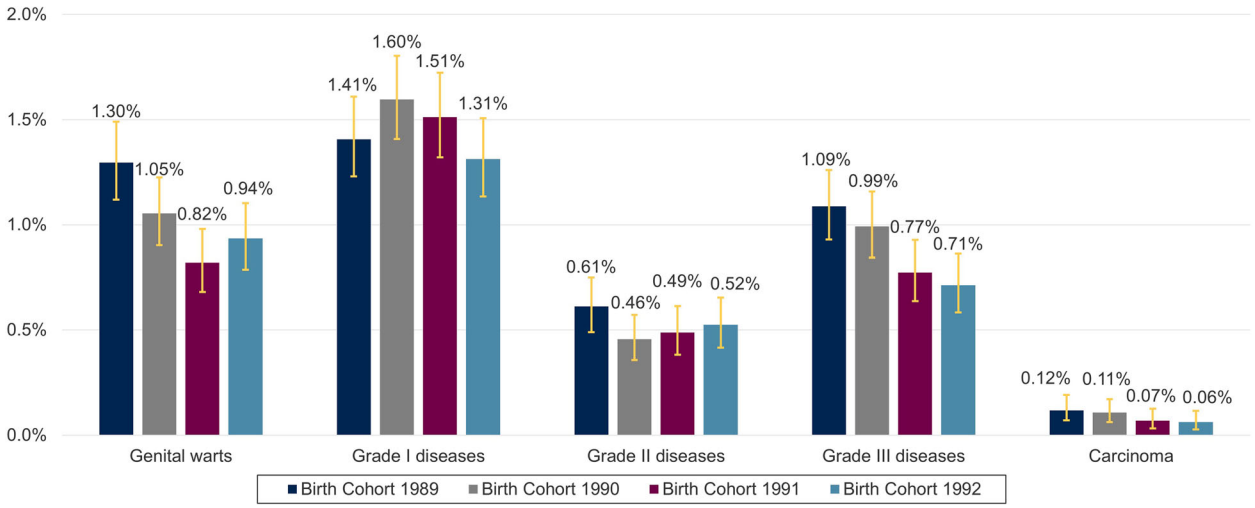

Fig. 2 Three-year APR of anogenital diseases in women 23–25 years in Germany from 2012 to 2017. APR = Administrative prevalence rate

Anogenital diseases grade II

Overall, the 3-year APR for anogenital diseases grade II remained stable over the four birth cohorts. It only decreased slightly from 0.61% (0.49–0.75) in birth cohort 1989 to 0.52% (0.42–0.65) in birth cohort 1992. Among the anogenital diseases grade II moderate cervical dysplasia (CIN II) was most frequently recorded. Moderate vaginal dysplasia (VAIN II) and moderate vulvar dysplasia (VIN II) were hardly recorded (Fig. 4). 1-year APR for grade II disease are summarized for individual age years in the ADDITIONAL FILE 1, Supplementary Figure 3.

Anogenital diseases grade III

The 3-year APR for anogenital diseases grade III decreased continuously from birth cohort 1989 (1.09% (0.93–1.26)) to birth cohort 1992 (0.71% (0.58–0,86)). Among the anogenital diseases grade III, severe cervical dysplasia was most frequently recorded and followed the trend of the pooled anogenital diseases grade III results.

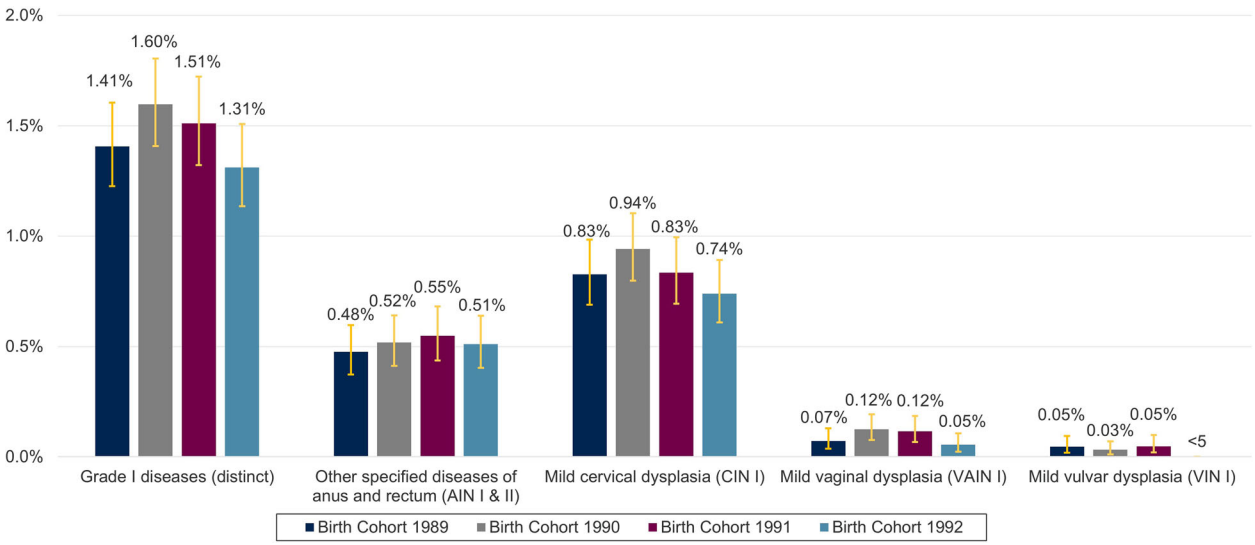

Fig. 3 Three-year APR of anogenital diseases grade I in 23–25-year-old women in Germany from 2012 to 2017**.** APR = Administrative prevalence rate; AIN = anal intraepithelial neoplasia; CIN = cervical intraepithelial neoplasia; VAIN = vaginal intraepithelial neoplasia; VIN = vulvar intraepithelial neoplasia. The figure shows the 3-year APR of anogenital diseases grade I (total and the subsets of conditions in grade I category). Please note, that AIN I & II are coded via the same ICD-10-GM code. Due to data protection regulations results for patients with $n < 5$ must not be reported and can constitute 1 to 4 patients

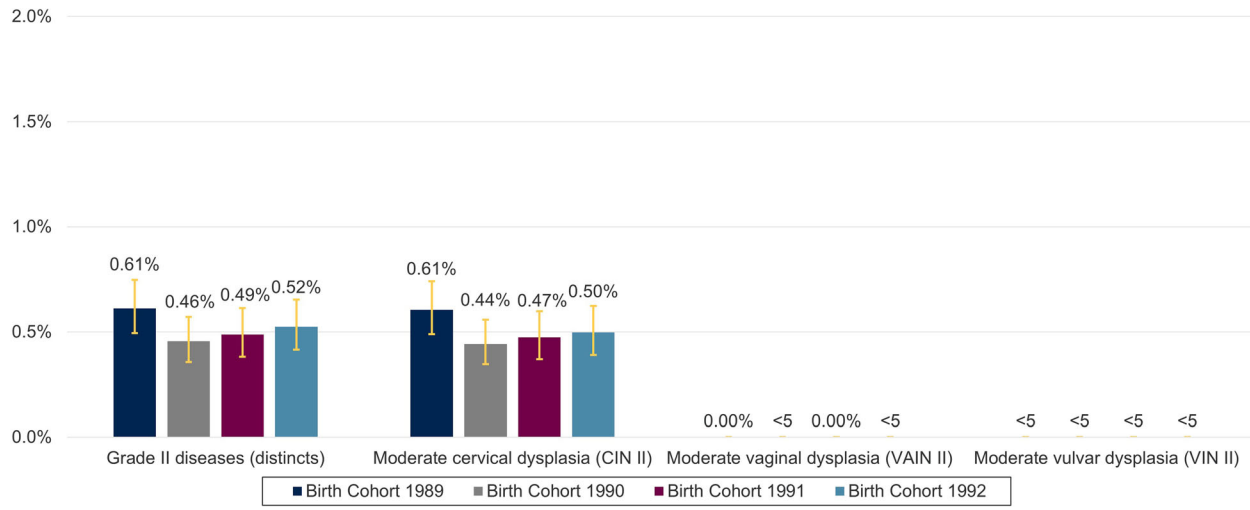

Fig. 4 Three-year APR of genital diseases grade II in 23–25-year-old women in Germany from 2012 to 2017. APR = Administrative prevalence rate; CIN = cervical intraepithelial neoplasia; VAIN = vaginal intraepithelial neoplasia; VIN = vulvar intraepithelial neoplasia. The figure shows the 3-year APR of anogenital diseases grade II (total and the subset of conditions in the grade II category). Due to data protection regulations results for patients with $n < 5$ must not be reported and can constitute 1 to 4 patients

(Fig. 5). 1-year APR for grade III disease are summarized for individual age years in the ADDITIONAL FILE 1, Supplementary Figure 4.

Invasive carcinoma

The 3-year APR for invasive carcinomas decreased from 0.12 to 0.06% (0.07–0.19 in birth cohort 1989 and 0.03–0.11 in birth cohort 1992) (Fig. 2). Malignant neoplasms of the cervix uteri were most frequently recorded and were responsible for almost all recorded diagnoses for carcinomas in all birth cohorts. Malignant neoplasms of anus and anal canal were not recorded in the analyzed birth cohorts.

Discussion

The aim of this study was to describe the burden of potentially HPV-related anogenital diseases in 23–25 old women after the introduction of HPV vaccination based on German administrative statutory health insurance claims data for the years 2012 to 2017. The three birth

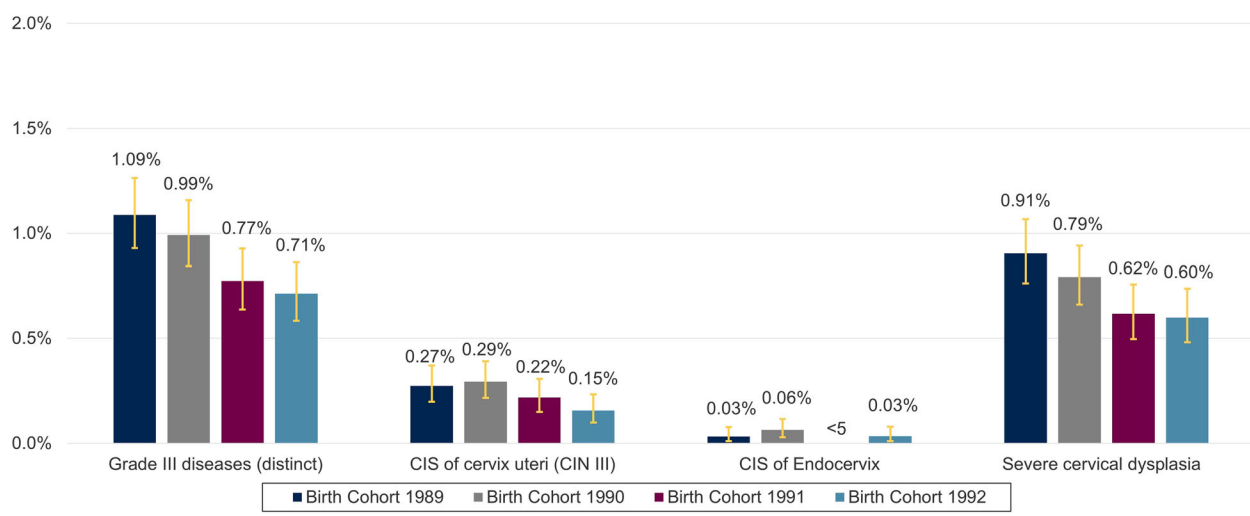

Fig. 5 Three-year APR of genital diseases grade III in 23–25-year-old women in Germany from 2012 to 2017. APR = Administrative prevalence rate, CIS = Carcinoma in situ, AIN = anal intraepithelial neoplasia; CIN = cervical intraepithelial neoplasia; VAIN = vaginal intraepithelial neoplasia; VIN = vulvar intraepithelial neoplasia. The figure shows the 3-year APR of anogenital diseases grade III (total and the subset of conditions in the grade III category). AIN III, VIN III, VAIN III, and other severe vaginal and vulvar dysplasia has been excluded from this figure as patient counts were either $n = 0$ or $n < 5$. Due to data protection regulations results for patients with $n < 5$ must not be reported and can constitute 1 to 4 patients

cohorts 1990 to 1992 were included, as they were fully eligible to receive HPV vaccination according to the first STIKO recommendation for HPV in 2007 and further birth cohort 1989, which was partially eligible (girls of birth cohort 1989, who turned 18 years old before March 23rd, 2007 exceeded the recommended age for vaccination in 2007). We found the highest administrative prevalence for anogenital diseases grade I, followed by genital warts and anogenital diseases grade III among all analyzed birth cohorts. A lower burden of anogenital disease potentially related to HPV was observed in the younger birth cohorts as compared to the older cohort. This was observed especially for genital warts and anogenital disease grade III.

The following section discusses the results in the context of HPV vaccination coverage in Germany. HPV vaccination status of the study population could not be evaluated, as the included birth cohort should have received their HPV vaccination in the years 2007 to 2010, which were not available for this analysis. For the analyzed birth cohorts two publications provide estimates on the HPV vaccination coverage. Hense et al. evaluated initiation of HPV vaccination in 2008 based on data from a statutory health insurance and reported 37% of 16 years old girls with at least one dose, which would overlap with birth cohort 1992. In the same publication rates were 33, 19 and 18% for 17-, 18-, and 19-year-old women, respectively (corresponding to birth cohorts 1992–1989) [19]. Delere et al. reported HPV vaccination coverage based on self-reported history of approximately 2000 women aged between 18 and 20 years old in 2010 (cohorts 1990–1992) with 48.5% for three doses and 60.2% for at least one dose [24]. While these figures are to be interpreted with caution as they most likely do not accurately represent the vaccination coverage of our study population in the analyzed time period, it might give three important estimates: 1) coverage rates for HPV vaccination in Germany were generally lower than in countries with vaccination programs in schools [21]. In Australia e.g., the three-dose vaccination coverage for girls turning 15 years of age was 79% in 2015 [25]. Hence, disease burden in birth cohorts eligible for HPV vaccination may still be higher than one might expect with a better vaccination coverage. 2) vaccination coverage increases from birth cohorts that were not entirely eligible for HPV vaccination according to STIKO to birth cohorts that were eligible. Since we found a downward trend in the 3-year APR for selected diagnoses in favor of the younger birth cohorts, it may be speculated that this is due to increasing HPV vaccine coverage in younger cohorts. We found the downward trend in the 3-year APR for genital warts and grade III dysplasia, but not for grade I and II dysplasia. While this might be due to the rather low HPV vaccination coverage in Germany, it might be also correlated with the HPV types that are covered by the vaccines. HPV types causing the majority of genital warts (approximately 90% caused by HPV 6/11) and a number of grade III cervical diseases (approximately 45% caused by HPV 16/18) were covered by HPV vaccines available during the observation period. Grade I disease, however, is caused to a lesser extent by types 6, 11, 16 and 18 [9]. It may be speculated that a vaccine effect might be masked in an analysis without selection for vaccine-HPV type-associated disease. And 3), also for birth cohort 1989, which was not entirely eligible for HPV vaccination according to STIKO recommendation, a coverage of approximately 18% was reported in 2008 [19]. This birth cohort turned 18 during the year 2007 and thus girls may have had the chance to receive the vaccination regularly before their birthday. Also, individual health insurances provided an extended reimbursement for HPV vaccination up to the age of 26, or the vaccine may have been purchased as self-payer. Hence, in none of the analyzed birth cohorts our prevalence rates for HPV diseases do reflect the anogenital disease burden in a population without HPV immunization. Therefore, no assumptions on burden of potentially HPV-related anogenital diseases in unvaccinated women between 23 and 25 years of age can be made.

This next section discusses the results in the context of previous studies on burden of HPV diseases in Germany. One previous German study examined HPV type prevalence [24] but has not investigated associated anogenital diseases. Further studies assessing the incidence of anogenital warts before and after the introduction of the HPV vaccination in German statutory health insurance members aged 10–79 years old reported the highest incidence of anogenital warts for the age group 20–24 years [4, 6, 26]. In 2010, incidence was 493 per 100,000 person years in 20–24 year old and 149 per 100,000 person years in 15–19 year old females [6]. In a population-based surveillance study conducted from 2009 to 2010 in Wolfsburg/Germany to investigate the burden of HPV infections and associated anogenital diseases in women who were born in 1988 or 1989 (and 1983/84), an incidence of 0.72% and a total life risk of 1.4% for genital warts was estimated for the cohort 1988/89 [27]. For the same cohort a prevalence of 0.83% for CIN II and 0.33% for CIN III diseases was detected [28]. The 3-year APR for anogenital warts of 1.30% and for grade III cervical dysplasia of 0.60% for birth cohort 1989 found in our study is generally in line with this dimension. In Australia an observational study based on clinical diagnoses reported a prevalence of genital warts of 18.4% in young women before the introduction of HPV vaccination [29]. On one hand, the remarkably lower burden in our study might be explained by the fact that our analyzes did not include a population in the pre-HPV-vaccine era, and on the other hand the use of

administrative claims data in our study may have resulted in an underestimation of diagnoses (see further discussion on limitations below). It is also important to note that our analysis only provides a snapshot of the APR of anogenital diseases in women of a selected, young age (23–25) and are not transferable to the prevalence rates of HPV-related anogenital diseases over the complete lifespan.

The following section discusses the results more specifically in the context of previous studies on HPV vaccination impact in Germany. Single previous reports focused on HPV vaccine impact in Germany and are in line with our results. Deleré et al. found a significant lower HPV 16/18 prevalence in vaccinated women suggesting first effects of the vaccination. Data from the German Pharmacoepidemiological Research Database (GePaRD) also demonstrated a decline of anogenital warts among males and females at the age of 14–24 comparing the timeframe prior to vaccination with the timeframe after vaccination. While the largest decrease (by 60%) was observed for women in the age group 16–20, the incidence ratio in women aged between 21 and 26 years was reduced by 10–20% [6]. In our study, genital warts have been reduced by 28% (from 1.30% in birth cohort 1989 to 0.94% in birth cohort 1992), and HPV related anogenital diseases grade III have been reduced by 35% (from 1.09% in birth cohort 1989 to 0.71 in birth cohort 1992).

This last section discusses further potential limitations of the study in detail, most inherent with the use of health insurance claims data. Claims data are primarily collected for reimbursement purposes. Therefore, only patients who seek physician treatment and cause reimbursement for the health insurance could be identified in the database. Patients without symptoms might not seek medical advice, individuals who do not participate in screening examinations might not be identified, and patients who treat their disease (e.g. genital warts) by themselves or ignore the condition are not recorded in the database. Therefore, this study only presents the administrative prevalence based on reimbursement data and not the clinical prevalence of potentially HPV-related anogenital diseases on a population level. Furthermore, Germany had an opportunistic cervical cancer screening beginning at the age of 20 and thus, most documented diagnoses of intraepithelial neoplasia most likely have been identified during screening and further work-up (cytologically or histologically). The annual and biannual cervical cancer screening participation rate in women 25–29 years old was reported with approximately 60 and 70% in 2011, respectively [30]. As not all women attend the screening program for cervical cancer it is likely that some of the diseases might not have been diagnosed and recorded by a physician. Therefore, our results might underestimate the true clinical prevalence of the assessed anogenital diseases in Germany for women between 23 and 25 years.

For the identification of potentially HPV related anogenital diseases we used ICD-10-GM codes, which is the official classification for the encoding of diagnoses in inpatient and outpatient medical care in Germany since 2000 [31]. Clinicians in the outpatient setting are required to add one of the following specifications to the ICD-10-GM codes: “suspected diagnosis”, “diagnosis ruled out”, “status post”, or “verified diagnosis”. For instance, “suspected” may be coded, if the physician is not certain about the presence of the coded disease and a confirming laboratory analysis is still pending. To ensure the accuracy of diagnoses only “verified” diagnoses in the outpatient and primary and secondary diagnoses in the inpatient sector were used. With this approach however, we excluded women who might be suspected to have one of the investigated anogenital diseases or women who have been cured from of the anogenital diseases (e.g. genital warts) and see their physician for a follow-up visit. This could have led to an underestimation of the APR. Additionally, we decided to only consider very specific ICD-10-GM codes potentially associated with HPV-related anogenital diseases, but physicians may use less specific codes. This might also have contributed to the underestimation of the true rate of clinical diagnoses.

Cervical cancer screening in Germany is Pap-based for women in their twenties. Documented diagnoses in our analysis are most likely cytologically or histologically defined. No laboratory data was available for this study to demonstrate an HPV association of anogenital diseases. Therefore, it is not possible to distinguish between anogenital diseases, which were caused by an HPV infection and those not caused by an HPV infection. However, it is expected that high-risk HPV infections cause almost all cervical cancers and precancers, approximately 90% of high-grade anal, vulvar and vaginal intraepithelial neoplasia and 30, 70 and 90% of vulvar, vaginal and anal cancers, respectively [9] and therefore, a very high rate of HPV association is expected for our captured diagnoses.

Finally, the instrument of ARP is subject to limitations that might influence the results of our study. Data on outcomes might be collected in different ways over time for the different study cohorts. Migration of populations affecting the study cohort might influence the differences between the groups. Seasonal or cyclical variations might result in fluctuations that affect the outcome trend. These limitations are assumed to be negligible in our study as we expect no major changes in the recording behavior of physicians during the study period and the impact of migration will not have affected the SHI, as medical services are paid by other payers [32]. Seasonal or cyclical variations in HPV types have not been reported in the literature so far.

Conclusions

In summary, our results demonstrate the highest administrative prevalence for anogenital diseases grade I, followed by genital warts and anogenital diseases grade III among all analyzed birth cohorts. Even though the HPV vaccination status of the study population was unknown, a decrease of the disease burden of genital warts and anogenital grade III disease was observed in favor of the younger birth cohorts who were fully eligible for HPV vaccination according to STIKO recommendation. Further research is necessary to confirm the observed trend including analyses linked to vaccination status.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12879-020-05002-w.

Additional file 1.

Abbreviations

AIN: Anal intraepithelial neoplasia; APR: Administrative prevalence rate; CIN: Cervical intraepithelial neoplasia; CIS: Carcinoma in situ; EMA: European Medicines Agency; GePaRD: German Pharmacoepidemiological Research Database; HPV: Human papillomavirus; ICD-10-GM: International Statistical Classification of Diseases, German Modification; InGef: Institute for Applied Health Research Berlin [Institut für Angewandte Gesundheitsforschung Berlin]; OTC: Over-the-counter; SHI: Statutory health insurance [Gesetzliche Krankenversicherung]; STIKO: German Standing Committee on Vaccination [Ständige Impfkommission]; VAIN: Vaginal intraepithelial neoplasia; VIN: Vulvar intraepithelial neoplasia; ZfKD: German Centre for Cancer Registry Data [Zentrum für Krebsregister Daten]

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Authors' contributions

MR, SM, RW, KS, CJ, and MH developed the study design. WG made substantial contributions to the acquisition of the data. KS, and CJ analyzed the dataset and drafted the manuscript. MR, SM, RW, KS, CJ, SB and MH interpreted the data and contributed to the development of the manuscript. All authors provided critical review and revision of drafts, and approval of the final manuscript.

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Availability of data and materials

The utilized database in this study is available from the Institute for Applied Health Research Berlin (InGef) but restrictions apply to the availability of these data. Access to the data is restricted to health service research and is granted on a study by study basis from the InGef on behalf of the participating statutory health insurances.

Ethics approval and consent to participate

This study used anonymized German claims data. Data contributing to the InGef Research Database are stored at a specialized data center according to §284 in combination with §70 and §71 Social Code Book ("Sozialgesetzbuch", SGB) V. Access to the data is restricted to health service research and is granted on a study by study basis from the InGef on behalf of the participating statutory health insurances. The data center is owned by statutory health insurances and provides data warehouse services. In the data center (acting as a trust center), data with respect to individual insured members and health care providers (e.g. physicians, practices, hospitals, pharmacies) are anonymized by coarsening or by removing individual variables. Since all patient-level data in the InGef Research Database are no longer social data according to § 67 Abs. 2 SGB X in combination with Art. 4 Nr. 1 of the General Data Protection Legislation ("Datenschutz-Grundverordnung", DSGVO), institutional review board/ethical approval and informed consent of the patient was not required. Furthermore, regions that are smaller than federal states or patient cohorts with less than 100 individuals were not analyzed in a granular way and patient counts below 5 were reported as "< 5".

Consent for publication

Not applicable.

Competing interests

MR, SM, and RW are full time employees of MSD SHARP & DOHME GmbH. KS, CJ, and SB are full-time employees of Xcenda, acting as contractors of MSD SHARP & DOHME GmbH for the execution of this study. MH received honoraria as speaker and member of medical advisory boards from MSD Sharp & Dohme GmbH, Astra Zeneca, Gedeon Richter and honoraria as an author for Thieme and Springer.

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Publisher's Note

Modul 8

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RESEARCH ARTICLE Open Access

Rates of pneumonia among children and adults with chronic medical conditions in Germany

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Abstract

Background: The objective of this study is to evaluate rates of all-cause pneumonia among "at-risk" and "high-risk" children and adults in Germany—in comparison with age-stratified healthy counterparts—during the period following the 2006 recommendation for universal immunization of infants with pneumococcal conjugate vaccine.

Methods: Retrospective cohort design and healthcare claims information for 3.4 M persons in Germany (2009–2012) were employed. Study population was stratified by age and risk profile (healthy, "at-risk" [with chronic medical conditions], and "high-risk" [immunocompromised]). At-risk and high-risk conditions, as well as episodes of all-cause pneumonia, were identified via diagnosis, procedure, and drug codes.

Results and discussion: Rates of all-cause pneumonia were 1.7 (95 % CI 1.7-1.8) to 2.5 (2.4-2.5) times higher among children and adults with at-risk conditions versus healthy counterparts, and 1.8 (1.8-1.9) to 4.1 (4.0-4.2) times higher among children and adults with high-risk conditions. Rates of all-cause pneumonia among at-risk persons increased in a graded and monotonic fashion with increasing numbers of conditions (i.e., risk stacking).

Conclusions: An increased risk for all-cause pneumonia in German children and adults with a spectrum of medical conditions persists in the era of widespread pneumococcal vaccination, and pneumonia risk in persons with ≥2 at-risk conditions is comparable or higher than those with high-risk conditions.

Keywords: *Streptococcus pneumoniae*, Pneumococcal infections, Pneumonia, Comorbidity, Germany

Background

Community-acquired pneumonia (CAP) is a frequent cause of hospitalization and death in Germany. The incidence of CAP has been estimated to be 3.7-10.1/1000 inhabitants [1], and over 259,000 German adults were estimated to have been hospitalized for CAP in 2013 [2]. Ewig and colleagues observed that the incidence of CAP increased with advancing age, and that overall in-hospital mortality of CAP patients was 14 %, with the highest mortality in persons with comorbid conditions; among persons with malignancies, dementia, and pulmonary diseases (other than chronic obstructive pulmonary disease [COPD]), mortality was more than two-fold higher than among those with no known underlying conditions. Importantly, mortality risk was highest in the first days after admission, suggesting that prevention strategies may be more important than therapeutic approaches to reduce mortality [3].

Streptococcus pneumoniae (pneumococcus) has been reported to be one of the most common causes of ambulatory, hospitalized, and severe pneumonia among adults throughout Europe [4, 5]. While it is widely recognized that persons with immunocompromising conditions, as well as those with certain chronic illnesses, were at increased risk of pneumococcal disease prior to the widespread introduction of seven-valent pneumococcal conjugate vaccine (PCV7) in the US and western Europe, recent assessments of disease risk in populations following mass vaccination of children with PCVs are limited. The indirect effect of childhood immunization

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has led to impressive declines in the incidence of invasive pneumococcal disease in US adults [6–11], but more variable herd effects in western Europe [12]. Further confirmation from additional populations as to the magnitude of the increased risk of pneumococcal disease associated with certain chronic medical conditions following introduction of pneumococcal conjugate vaccines would be valuable for developing future vaccine policies for the prevention of pneumonia.

We therefore employed a large German research database to estimate rates of all-cause pneumonia—as a proxy for pneumococcal disease—among persons with and without one or more of the chronic illnesses included by the German Committee on Vaccination (Ständige Impfkommission [STIKO]) and/or the US Advisory Committee for Immunization Practices (ACIP) as indications for pneumococcal vaccination. We also examined disease rates among persons with other conditions that might increase infection risk based on limited data from other studies, including three autoimmune diseases—rheumatoid arthritis, systemic lupus erythematosus, and Crohn's disease—as well as neuromuscular (chiefly cerebral palsy)/seizure disorders [13–16]. Finally, we examined the impact of risk stacking among the at-risk population by estimating disease rates within subgroups defined on the basis of the number of concurrent conditions.

Methods

Data design and source

A retrospective cohort design and data from the Health Risk Institute (HRI) Research Database spanning 2008–2012 were employed. The HRI Database comprises medical and drug claims from an age and gender representative sample of 3.4 million persons covered by the statutory health care system in Germany, approximately 4 % of the total population. The HRI Scientific Board approved our study and granted access to the HRI Research Database.

Data available from each medical claim include date/quarter of service, place of service, diagnoses (International Statistical Classification of Diseases and Related Health Problems, 10th revision, German Modification [ICD-10-GM]), procedures performed/services rendered, and quantity of services. Data available for each drug claim include the agent dispensed (as set forth by the Anatomical Therapeutic Chemical [ATC] System), dispensing/prescription date, and quantity dispensed. Medical and drug claims also include amounts paid (i.e., reimbursed) to providers by health insurers. Selected demographic and eligibility information (including age/year of birth, sex, dates of enrollment) also is available for persons in the HRI Database. All data can be arrayed to provide a detailed chronology of medical and pharmacy series used by each insured member over time.

Insurance benefits extend to all healthcare services. The HRI Database does not include data on clinical parameters (e.g., lab results), quality of life, or markers of disease severity because health insurers in Germany are prohibited by federal law from having such information. All patient-level data in the HRI Research Database are de-identified to comply with German data protection regulations. Use of the study database for health services research is therefore fully compliant with German federal law and, accordingly, IRB/ethical approval was not needed.

Study population

The study population comprised persons who were enrolled in a health insurer represented in the HRI Database on January 1, 2009. Persons who were not continuously eligible for health insurance benefits for at least one year prior to January 1, 2009 were excluded from the study population; less than 0.5 % of the population from the HRI Database was excluded due to this criterion. Infants <12 months of age as of this date were not subject to this exclusionary criterion.

Study subjects were stratified based on their age (<5, 5–17, 18–49, 50–59, and ≥60 years) and risk profile ("at-risk", "high-risk", and "healthy"). Risk profiles were defined based on the presence of medical conditions that are indications for pneumococcal vaccination among children and adults including alcoholism, asthma, chronic heart disease, chronic liver disease, chronic lung disease, chronic renal failure, cochlear implant, Crohn's disease, diabetes, Down's syndrome, functional/anatomic asplenia, HIV, immunosuppressant therapy, short gestation/low birthweight, smoking, as well as those medical conditions hypothesized to be associated with increased risk including neuromuscular/seizure disorders, rheumatoid arthritis, and systemic lupus erythematosis [13–16]. The list of medical conditions was based on recommendations for vaccination set forth by STIKO and/or ACIP, as well as other conditions previously reported to confer an increased risk of pneumococcal disease.

Immunocompetent persons with ≥1 chronic medical condition were classified as at-risk; immunocompromised/immunosuppressed persons and those with a cochlear implant were classified as high-risk. At-risk and high-risk were mutually exclusive categories and thus, for example, persons considered immunosuppressed due to cancer treatment were included in the high-risk category only, even if they also had an at-risk condition. Persons without evidence of at-risk or high-risk conditions were classified as healthy. At-risk and high-risk medical conditions were ascertained using ICD-10-GM diagnosis codes recorded any time prior to the beginning of the 2009 calendar year. Operational

algorithms employed to identify at-risk and high-risk conditions are available in Additional file 1: Table S1 and Additional file 2: Table S2, respectively, of the online supplement.

Study measures

Episodes of all-cause pneumonia (i.e., all clinical cases caused by all known and unknown pathogens, including *S. pneumoniae*) were identified during the four-year period beginning on January 1, 2009 and ending on December 31, 2012 or the date of health insurer disenrollment, whichever occurred first. Episodes were identified using operational algorithms based on corresponding diagnosis codes (ICD-10-GM) in the principal or secondary position, procedure codes for inpatient care (Operationen- und Prozedurenschlüssel [OPS]), and ATC drug codes, as set forth in the online supplement (Additional file 3: Table S3); cases that were invasive (i.e., bacteremic) in nature were excluded from consideration. Multiple episodes of all-cause pneumonia for a given patient were included as independent events if they were separated by ≥90 days.

Statistical analyses

Incidence rates of all-cause pneumonia episodes were estimated for children and adults within each age group by risk profile as well as individual medical condition, and were expressed per 100,000 person-years. Rate ratios for disease episodes among persons with at-risk and high-risk conditions, respectively—overall and by individual medical condition—versus their age-stratified healthy counterparts were estimated using Poisson regression (SAS v 9.3). Rates of disease and corresponding rate ratios (vs. healthy counterparts) also were calculated for at-risk persons by the number of at-risk conditions.

Results

Children

Characteristics

Children aged <5 years and 5–17 years contributed a total of 0.5 million and 1.7 million person-years of observation, respectively. In these two age groups, 71 % and 79 %, respectively, had none of the selected chronic or immunocompromising conditions, 26 % and 19 % had ≥1 at-risk condition (and no high-risk conditions), and 3 % and 2 % had a high-risk condition.

Among those with at-risk conditions, chronic lung disease (68 % and 54 %) and asthma (23 % and 43 %) were common; 17 % of children <5 years of age and 13 % of children 5–17 years of age with at-risk conditions had more than one condition.

Disease rates

Rates of all-cause pneumonia among children <5 years and 5–17 years of age with at-risk conditions were 1.7 (95 % confidence interval [CI] 1.7-1.8) and 2.4 (2.3-2.5) times the rates in their healthy counterparts, and rates of all-cause pneumonia among high-risk children in these age groups were 1.8 (1.8-1.9) and 2.9 (2.8-3.0) times the rates in children without at-risk or high-risk conditions (Table 1). Rate ratios for all-cause pneumonia among children with at-risk conditions increased with the number of such conditions compared with healthy counterparts (Fig. 1). Among younger children, rate ratios increased from 1.5 (1.5-1.5) for those with one condition to 4.7 (4.6-4.7) for those with ≥3 conditions; among older children, rate ratios increased from 2.0 (1.9-2.1) to 11.3 (11.0-11.5).

Adults

Characteristics

Persons aged 18–49 years, 50–59 years, and ≥60 years contributed a total of 5.7 million, 2.0 million, and 3.5 million person-years of observation, respectively. Approximately 76 %, 60 %, and 36 %, respectively, had none of the selected chronic or immunocompromising conditions. The prevalence of at-risk and high-risk conditions increased with increasing age: 21 %, 33 %, and 45 % had at-risk conditions, and 3 %, 7 %, and 19 % had high-risk conditions.

Among adults aged 18–49 years with at-risk conditions, the most common conditions were chronic lung disease (48 %), asthma (27 %), and chronic liver disease (13 %). In adults 50–59 years of age, the most common conditions were chronic lung disease (37 %), diabetes (26 %), chronic liver disease (24 %), and chronic heart disease (23 %). In adults ≥60 years of age, the most common conditions were chronic heart disease (46 %), diabetes (41 %), chronic lung disease (30 %), and chronic liver disease (20 %).

Disease rates

Adults aged 18–49, 50–59, and ≥60 years with at-risk conditions had 2.2 (2.1-2.4), 2.3 (2.2-2.4), and 2.5 (2.4-2.5) times the rates of all-cause pneumonia as their healthy counterparts (Table 2). Corresponding rate ratios for those with high-risk conditions were 3.2 (3.0-3.4), 3.7 (3.6-3.9), and 4.1 (4.0-4.2).

Rate ratios for all-cause pneumonia among adults with at-risk conditions increased with the number of such conditions compared with healthy counterparts (Fig. 2). Rates among adults with two at-risk conditions were generally similar to rates among adults with high-risk conditions, and rates in adults with three or more at-risk conditions were higher than those among adults with high-risk conditions. Rates and rate ratios of all-cause pneumonia among healthy, at-risk, and high-risk adults stratified by additional age groups are available in Additional file 4: Table S4 of the online supplement.

Table 1 Rates of all-cause pneumonia among healthy, at-risk, and high-risk children

	No. of Person-Years		All-Cause Pneumonia			
			Age <5 Years		Age 5–17 Years	
	Age <5 Years	Age 5-17 Years	Rate per 100 K	Rate Ratios[a] (95 % CI)	Rate per 100 K	Rate Ratios[a] (95 % CI)
Risk Group						
Healthy	360,184	1,318,738	3,779	1.0	730	1.0
At-Risk	129,895	310,546	6,555	1.7 (1.7, 1.8)	1,734	2.4 (2.3, 2.5)
Chronic heart disease	15,181	19,899	7,813	2.1 (2.0, 2.1)	2,055	2.8 (2.7, 2.9)
Chronic lung disease	88,323	169,241	6,539	1.7 (1.7, 1.8)	1,836	2.5 (2.4, 2.6)
Diabetes	680	5,595	5,886	1.6 (1.5, 1.6)	1,734	2.4 (2.3, 2.5)
Asthma	29,737	134,188	8,986	2.4 (2.3, 2.4)	1,994	2.7 (2.6, 2.9)
Alcoholism	0	2,092	0	0.0 (——)	813	1.1 (1.0, 1.2)
Chronic liver disease	241	2,074	14,099	3.7 (3.7, 3.8)	2,941	4.0 (3.9, 4.2)
Smokers	0	530	0	0.0 (——)	1,321	1.8 (1.7, 1.9)
Down's syndrome	473	1,318	14,579	3.9 (3.8, 3.9)	4,022	5.5 (5.3, 5.7)
Neuromuscular/seizure disorder	9,075	18,219	7,570	2.0 (2.0, 2.0)	2,898	4.0 (3.8, 4.1)
Short gestation/low birthweight	10,311	32	8,719	2.3 (2.3, 2.4)	6,250	8.6 (8.4, 8.8)
Rheumatoid	67	1,250	10,448	2.8 (2.7, 2.8)	960	1.3 (1.2, 1.4)
Rheumatoid arthritis	8	358	0	0.0 (——)	280	0.4 (0.3, 0.4)
Lupus	0	59	0	0.0 (——)	0	0.0 (——)
Crohn's	59	841	11,865	3.1 (3.1, 3.2)	1,307	1.8 (1.7, 1.9)
High-Risk	17,704	45,383	6,914	1.8 (1.8, 1.9)	2,131	2.9 (2.8, 3.0)
Cochlear implant	1,134	2,684	5,907	1.6 (1.5, 1.6)	2,906	4.0 (3.8, 4.1)
Functional/anatomic asplenia	850	2,347	9,175	2.4 (2.4, 2.5)	2,983	4.1 (3.9, 4.2)
HIV	318	1,287	3,769	1.0 (1.0, 1.0)	1,710	2.3 (2.2, 2.5)
Chronic renal failure	1,127	4,579	12,778	3.4 (3.3, 3.4)	3,036	4.2 (4.0, 4.3)
Immunosuppressants	905	4,893	9,720	2.6 (2.5, 2.6)	1,696	2.3 (2.2, 2.4)
Malignant neoplasms	854	4,669	7,263	1.9 (1.9, 2.0)	1,328	1.8 (1.7, 1.9)
Solid organ transplantation	76	326	34,354	9.1 (9.0, 9.2)	6,441	8.8 (8.6, 9.0)
Congenital immunodeficiency	13,227	29,420	6,328	1.7 (1.6, 1.7)	2,094	2.9 (2.7, 3.0)
Diseases of white blood cells	683	1,468	11,267	3.0 (2.9, 3.0)	2,247	3.1 (3.0, 3.2)

[a]Relative to healthy counterparts

Discussion

We undertook a large retrospective evaluation of rates of all-cause pneumonia among "at-risk" and "high-risk" children and adults in Germany—in comparison with age-stratified healthy counterparts—in the period following the 2006 recommendation for universal immunization of infants with pneumococcal conjugate vaccine. The results of this evaluation suggest that immunocompetent persons with comorbid conditions and immunocompromised persons of all ages continue to suffer a disproportionate burden of pneumonia in the era of widespread pneumococcal vaccination [3, 17–21]. Both the proportion of the German population with an at-risk or high-risk condition and the incidence of CAP are reported to climb with increasing age. Moreover, the results of this study suggest that the risk of all-cause pneumonia among children and adults with ≥2 at-risk conditions is comparable to, or exceeds, corresponding values among age-stratified persons with high-risk conditions. Our data also provide additional evidence in support of an increased risk of all-cause pneumonia in adults with rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, and neuromuscular/seizure disorders [13, 22]. Such conditions are not currently included within the STIKO or ACIP recommendations for prevention.

Notwithstanding differences in study design and methods between our evaluation and work by Ewig and colleagues—including their use of records from all hospitals in Germany (vs. claims information from an age/gender-representative sample in our study), their

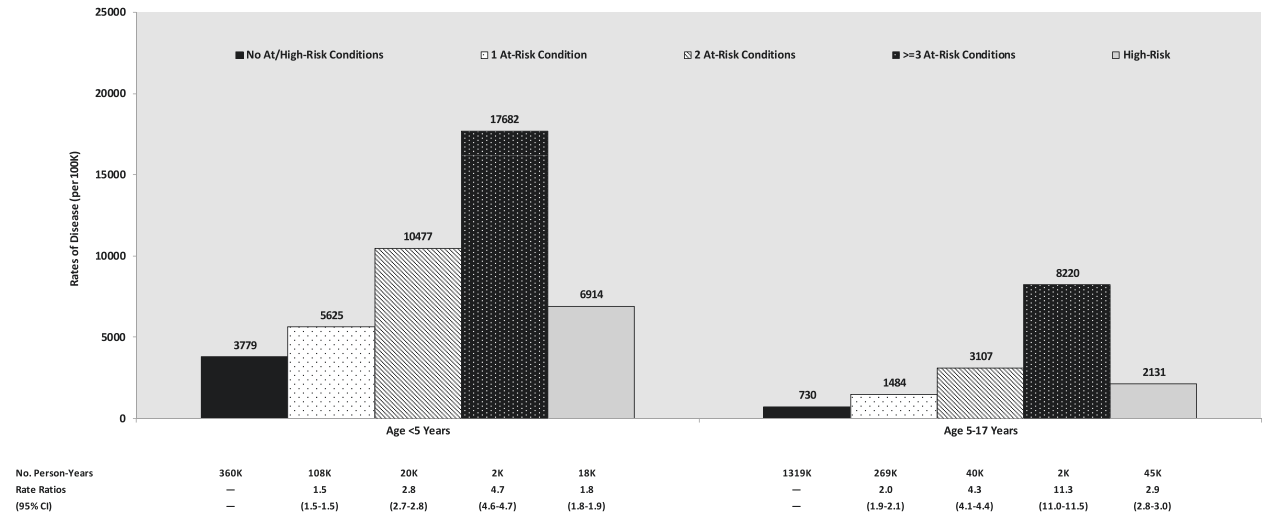

Fig. 1 Rates of all-cause pneumonia among children by number of risk conditions

focus on an adult population (vs. children and adults), and their focus on inpatient CAP (vs. inpatient and outpatient all-cause pneumonia)—the results of our study are largely consistent with their findings. Ewig et al. identified cardiac, central nervous system, and pulmonary disease (other than COPD), as well as diabetes and COPD, as the five most prevalent comorbid conditions in adults with hospitalized CAP. Similarly, we found chronic lung disease, chronic heart disease, and diabetes to be the most prevalent chronic diseases among Germans with all-cause pneumonia; asthma and chronic liver disease also were found to be common among pneumonia cases.

Recent studies from the UK and US found that the elevated risk of pneumonia in adults with selected medical conditions persisted during the era following the introduction of pneumococcal conjugate vaccine, although the magnitude of relative risk was not always consistent [13, 22–24]. In our study, German children under the age of 5 years with at-risk conditions accounted for 26 % of this age cohort yet 36 % of all-cause pneumonia cases; children aged 5–17 years with at-risk conditions accounted for 19 % of this cohort but 34 % of all-cause pneumonia cases. Comparable results for adults aged <60 years were: 18–49 year-olds, 21 % of the cohort and 35 % of disease burden; 50–59 year-olds, 33 % of the cohort and 47 % of disease burden. Consistent with published data from Shea and colleagues, we found increasing incidence of pneumonia with increasing age in at-risk, high-risk, and healthy persons, and relatively stable rate ratios, suggesting that the relative increase in disease risk with age is similar in all three groups [13].

We chose all-cause pneumonia as a proxy for pneumococcal pneumonia based on several considerations. First, studies in children demonstrate that identification of pneumococcus as a cause of hospitalized pneumonia substantially underestimates the role of pneumococcus compared to the reduction in all-cause hospitalized pneumonia achieved following introduction of pneumococcal conjugate vaccine [25, 26]. We believe the same challenge would be relevant for the diagnosis of pneumococcal pneumonia in adults in clinical settings. Moreover, operational algorithms for pathogen-specific cases of pneumonia based on diagnosis codes typically lack adequate sensitivity since diagnostic tests (i.e., culture, serological, and polymerase chain reaction [PCR] tests, as well as invasive sampling methods) are infrequently performed in clinical practice. Thus, in the absence of concurrent bacteremia, the diagnosis (and therefore coding) of pneumococcal pneumonia underestimates disease burden. Second, in the control group in the CAPiTA study, 22 % (174 of 787) of episodes of CAP in adults ≥65 years of age were due to vaccine serotypes representing a minimum estimate of pneumococcal burden in this age group as nonvaccine serotypes were not sought. Lastly, in the retrospective study by Shea and colleagues based on US healthcare claims data, the increased disease risk in “at-risk” and “high-risk” subjects was comparable for both all-cause pneumonia and pneumococcal pneumonia [13].

We note several other limitations that are inherent in the use of healthcare claims data for retrospective studies such as this one. First, rates of all-cause pneumonia may be misestimated somewhat due to the less than perfect sensitivity and specificity of our case-ascertainment algorithm. However, to the extent this limitation impacts rates in a proportional manner across age and risk groups, rate ratios should be largely unaffected. Second, use of operational algorithms and the left-truncation of

Table 2 Rates of all-cause pneumonia among healthy, at-risk, and high-risk adults

				All-Cause Pneumonia					
	No. of Person-Years			Age 18–49 Years		Age 50–59 Years		Age ≥60 Years	
	Age 18-49 Years	Age 50-59 Years	Age ≥60 Years	Rate per 100 K	Rate Ratios[a] (95 % CI)	Rate per 100 K	Rate Ratios[a] (95 % CI)	Rate per 100 K	Rate Ratios[a] (95 % CI)
Risk Group									
Healthy	4,334,344	1,194,431	1,308,873	441		684		1,439	
At-Risk	1,197,718	648,276	1,575,635	975	2.2 (2.1, 2.4)	1,554	2.3 (2.2, 2.4)	3,547	2.5 (2.4, 2.5)
Chronic heart disease	116,350	145,449	703,271	1,147	2.6 (2.5, 2.8)	1,780	2.6 (2.5, 2.7)	4,451	3.1 (3.0, 3.2)
Chronic lung disease	579,980	238,260	466,695	1,088	2.5 (2.3, 2.6)	2,195	3.2 (3.1, 3.3)	5,246	3.6 (3.5, 3.7)
Diabetes	97,028	165,443	643,437	1,115	2.5 (2.4, 2.7)	1,592	2.3 (2.2, 2.4)	3,736	2.6 (2.5, 2.7)
Asthma	323,267	102,513	165,056	1,112	2.5 (2.4, 2.7)	2,314	3.4 (3.2, 3.5)	4,621	3.2 (3.1, 3.3)
Alcoholism	33,593	25,488	27,142	1,578	3.6 (3.4, 3.8)	2,754	4.0 (3.9, 4.2)	5,626	3.9 (3.8, 4.0)
Chronic liver disease	154,804	154,616	321,444	1,015	2.3 (2.2, 2.5)	1,419	2.1 (2.0, 2.2)	2,861	2.0 (1.9, 2.1)
Smokers	38,316	22,141	19,819	1,133	2.6 (2.4, 2.7)	2,529	3.7 (3.6, 3.8)	5,535	3.8 (3.7, 3.9)
Down's syndrome	2,926	451	139	2,016	4.6 (4.4, 4.8)	7,987	11.7 (11.4, 11.9)	11,471	8.0 (7.8, 8.1)
Neuromuscular/seizure disorder	49,368	18,445	36,733	1,669	3.8 (3.6, 4.0)	2,483	3.6 (3.5, 3.8)	6,711	4.7 (4.6, 4.8)
Short gestation/low birthweight	1,607	0	4	622	1.4 (1.3, 1.5)	0	0.0 (——)	0	00.0 (——)
Rheumatoid	48,367	35,563	83,318	1,164	2.6 (2.5, 2.8)	1,696	2.5 (2.4, 2.6)	3,842	2.7 (2.6, 2.8)
Rheumatoid arthritis	26,323	28,126	76,319	1,193	2.7 (2.6, 2.9)	1,582	2.3 (2.2, 2.4)	3,830	2.7 (2.6, 2.7)
Lupus	1,624	794	1,028	2,402	5.5 (5.2, 5.7)	3,777	5.5 (5.3, 5.7)	5,640	3.9 (3.8, 4.0)
Crohn's	21,202	7,128	6,633	990	2.2 (2.1, 2.4)	1,796	2.6 (2.5, 2.7)	3,317	2.3 (2.2, 2.4)
High-Risk	181,558	132,436	630,789	1,411	3.2 (3.0, 3.4)	2,559	3.7 (3.6, 3.9)	5,852	4.1 (4.0, 4.2)
Cochlear implant	719	542	2,787	1,669	3.8 (3.6, 4.0)	2,768	4.0 (3.9, 4.2)	4,629	3.2 (3.1, 3.3)
Functional/anatomic asplenia	11,350	3,580	8,583	1,665	3.8 (3.6, 4.0)	4,134	6.0 (5.9, 6.2)	9,705	6.7 (6.6, 6.9)
HIV	7,940	2,692	7,386	1,952	4.4 (4.2, 4.6)	2,192	3.2 (3.1, 3.3)	3,994	2.8 (2.7, 2.9)
Chronic renal failure	38,170	36,522	266,953	1,776	4.0 (3.8, 4.2)	3,313	4.8 (4.7, 5.0)	8,114	5.6 (5.5, 5.8)
Immunosuppressants	84,727	81,587	381,069	1,779	4.0 (3.9, 4.2)	2,787	4.1 (3.9, 4.2)	5,053	3.5 (3.4, 3.6)
Malignant neoplasms	82,755	80,199	379,086	1,556	3.5 (3.4, 3.7)	2,557	3.7 (3.6, 3.9)	4,957	3.4 (3.4, 3.5)
Solid organ transplantation	2,574	1,850	2,924	8,509	19.3 (18.9, 19.7)	12,056	17.6 (17.3, 17.9)	15,768	11.0 (10.8, 11.1)
Congenital immunodeficiency	38,927	10,800	16,179	1,123	2.5 (2.4, 2.7)	2,935	4.3 (4.1, 4.4)	6,385	4.4 (4.3, 4.5)
Diseases of white blood cells	9,468	5,779	13,734	1,986	4.5 (4.3, 4.7)	3,063	4.5 (4.3, 4.6)	6,407	4.5 (4.3, 4.6)

[a]Relative to healthy counterparts

the study database undoubtedly resulted in the misclassification of risk profiles for some persons, including both errors of omission and commission. For example, diagnosis codes capturing smoking and alcoholism are under-recorded in the study database, and procedures (e.g., cochlear implant) performed prior to the beginning of the study database were not observable. Unfortunately, it was not possible to undertake a formal evaluation—for example, via chart review or use of additional data sources (e.g., electronic medical records)—of the accuracy of these algorithms within the context of this study. Third, data limitations precluded us from identifying the specific pathogen/serotype causing disease; it would be of interest to know the proportion of cases due to individual pathogens/serotypes, and whether or not they are included in PCV7, PCV10, PCV13, and PPSV23 (or currently unavailable vaccines). Fourth, to the extent pneumococcal vaccination status varies by risk profile (i.e., likely to be higher uptake among high-risk and at-risk persons vs. healthy persons), rate ratios may be downwardly biased. Fifth, while the HRI Database comprises claims data from individuals covered by the German statutory health care system and is representative of the German population in terms of age and gender, it is unknown whether the HRI Database is representative of the German population in terms of race,

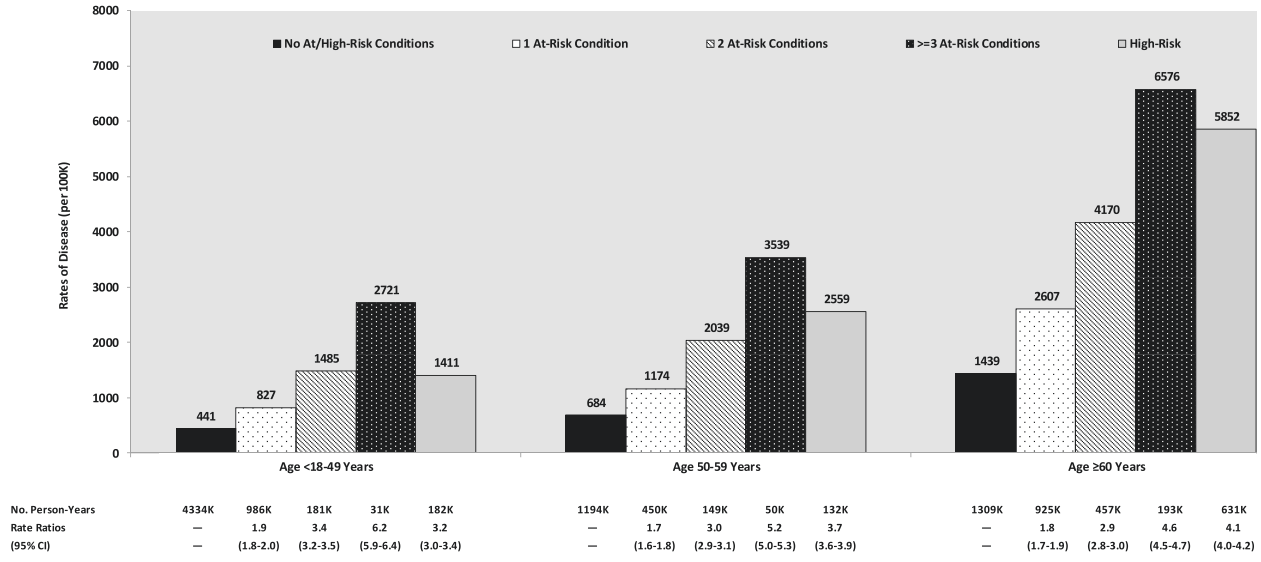

Fig. 2 Rates of all-cause pneumonia among adults by number of risk conditions

socio-economic factors, and other such characteristics. Finally, while the HRI Research Database should be sufficiently large to compare (robustly) rates of disease between age-specific at-risk and high-risk persons versus their healthy counterparts, comparisons of rates within subgroups defined on the basis of individual conditions are undoubtedly underpowered in many instances and should be interpreted with caution.

Conclusion

Our data confirm previous reports of enhanced risk in individuals with multiple comorbid conditions [13, 22, 27]. Expanded use of pneumococcal conjugate vaccines have been proposed to prevent pneumococcal pneumonia in high-risk individuals and those 65 years of age and older. In conjunction with recent publications [11, 13, 22, 23, 28], our findings suggest that the highest rates of all-cause pneumonia, and presumably pneumococcal pneumonia, occur in individuals with multiple comorbid conditions in the absence of immune deficiency. In adults with traditional high-risk conditions, high mortality rates have been reported [3]. If high mortality rates from all-cause pneumonia and pneumococcal pneumonia also are observed in individuals with multiple at-risk conditions in the absence of immune compromise, further effort to understand the underlying susceptibility could lead to additional strategies for prevention.

Additional files

Additional file 1: Table S1. Diagnosis, procedure, and drug codes for algorithms identifying at-risk conditions. (DOC 91 kb)

Additional file 2: Table S2. High risk-conditions: Diagnosis, procedure, and drug codes for algorithms identifying baseline risk factors and study measures. (DOC 70 kb)

Additional file 3: Table S3. Outcome: Diagnosis, procedure, and drug codes for algorithms identifying all-cause pneumonia *. (DOC 97 kb)

Additional file 4: Table S4. Rates of all-cause pneumonia among healthy, at-risk, and high-risk adults, by age. (DOC 941 kb)

Abbreviations

ATC: Anatomic Therapeutic Chemical; COPD: Chronic obstructive pulmonary disease; CAP: Community-acquired pneumonia; HRI: Health Risk Institute; ICD-10-GM: International Statistical Classification of Diseases and Related Health Problem, 10th revision, German Modification; OPS: Operationen- und Prozedurenschlüssel; OPS: Polymerase Chain Reaction; PCR: Pneumococcal conjugate vaccine; PCV7: Seven-valent pneumococcal conjugate vaccine; STIKO: Ständige Impfkommission; pneumococcus: *Streptococcus pneumoniae*; PCV10: Ten-valent pneumococcal conjugate vaccine; PCV13: Thirteen-valent pneumococcal conjugate vaccine; PPSV23: Twenty-three-valent pneumococcal polysaccharide vaccine; ACIP: US Advisory Committee for Immunization Practices.

Competing interests

Funding for this research was provided by Pfizer Inc. to Policy Analysis Inc. (PAI) and Xcenda GmbH.

Authors' contributions

Authorship was designated based on guidelines promulgated by the International Committee of Medical Journal Editors (2004). All persons who met criteria for authorship were listed as authors on the title page. RAF, RK, SIP, DRS, and DW contributed to the conception and design of the study, SB and CJ acquired the data, and all authors participated in analysis or interpretation of the data. ESG, SIP, and DW prepared the manuscript, and SB, RAF, CJ, RK, KMS, and DRS provided critical review. All authors have read and approved the final version of the manuscript.

Acknowledgements

The study sponsor, Pfizer Inc., reviewed the study research plan and study manuscript; data management, processing, and analyses were conducted by PAI and Xcenda in cooperation with Elsevier Health Analytics, and all final analytic decisions were made by study investigators. Stephen I. Pelton confirms that he had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Vaccination rates and adherence in pneumococcal conjugate vaccination in mature born infants before and after vaccination schedule change – A claims database analysis

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Vaccination rates and adherence in pneumococcal conjugate vaccination in mature born infants before and after vaccination schedule change – A claims database analysis

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ABSTRACT

Background: In August 2015, the German Standing Committee on Vaccination (STIKO) changed the pneumococcal conjugate vaccination (PCV) schedule for mature infants from a 3+1 scheme to a 2+1 scheme. It was expected that a reduction of doses would be associated with a higher acceptance of the vaccination. Aim of this study was to assess vaccination rates and adherence for PCV after the change of recommendation based on real-world data.

Methods: A retrospective claims data analysis using the InGef Research Database was conducted. The study population consisted of all mature infants born in 2013 (last birth cohort completely under 3+1 recommendation) or 2016 (first birth cohort completely under 2+1 recommendation) with an individual follow-up of 24 months. Hexavalent combination vaccination (HEXA) with a consistent 3+1 recommendation was analyzed as reference.

Results: After follow-up of 24 months, 90.9% (91.2%) of the 2016 (2013) cohort received at least one dose of PCV. At the same age, 67.7% of the 2013 cohort received a booster dose according to the 3+1 schedule and 75.6% of the 2016 cohort received a booster dose presumably either according to the 2+1 (71.7%) or 3+1 (3.9%) schedule. Of those receiving the booster dose, only 46.3% (2016) and 45.1% (2013) received the booster dose on time as recommended. The HEXA vaccination rate increased from 88.9% (2013) to 91.6% (2016) with a full series completion in 69.1% (2013) vs 72.9% (2016). The proportion of infants receiving the booster vaccination on time rose to 50.0% in 2016 (47.8% in 2013).

Conclusions: Although the rate for the PCV booster dose slightly increased, nearly a quarter of the infants born in 2016 did not receive a booster dose at all. Furthermore, vaccinations were still frequently delayed, and the rate of unvaccinated infants remained constant.

1. Introduction

According to the World Health Organization (WHO), *Streptococcus pneumoniae* is one of the most important bacterial pathogens worldwide. Children less than five years of age, the elderly, and individuals with certain underlying diseases are particularly at risk [1,2]. Prior to the introduction of a general recommendation for vaccination against pneumococcal diseases, each year approximately 970 children less than five years of age suffered from invasive pneumococcal diseases (IPD) in Germany. 15% of IPD cases led to consequential sequalae, 1–10% of IPD cases were fatal [3]. In Germany, vaccine reimbursement is based on vaccination recommendations, updated annually by the German Standing Committee on Vaccination (STIKO). Since July 2006, vaccination with a pneumococcal conjugate vaccine is recommended by the STIKO for all children up to the age of 24 months in Germany. Immunization included 4 doses: a single dose should be administered at 2, 3, 4 months of age (MoA) and 11–14 MoA [4]. In August 2015, the STIKO released a new recommendation for pneumococcal conjugate vaccination (PCV) in mature infants including an immunization with 3 doses (2+1). A single dose should be administered at the age of 2, 4 and 11–14 MoA. For premature infants the 3+1 recommendation remained. One major rationale was that a reduction in the recommended doses might lead to a higher acceptance for

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vaccination and thus higher vaccination rates. As it was assumed that the effectiveness of the 2+1 schedule is potentially lower compared to the 3+1 schedule (91% vs 97%, respectively), the occurrence of approximately 20 additional cases of IPD in children less than five years of age could not be ruled out. In premature infants, the vaccination scheme did not change and remains 3+1 doses for full immunization [5].

In contrast to the Immunization Information Systems as defined by the US Centers for Disease Control and Prevention [6], the surveillance of vaccinations in Germany only provides aggregated data on vaccination rates, completeness, and timeliness [7], meaning that individual vaccination careers are not traceable with the publicly available data. Since 2008, the vaccination status against pneumococci (number and date of applied doses for each recommended vaccine according to the STIKO) is collected based upon the information available on the vaccination certificate during the school entry examination [8]. As of 2004, population-based vaccination-related claims data from the Association of Statutory Health Insurance Physicians ("Kassenärztliche Vereinigungen" - KV) were additionally analyzed within the project "KV vaccination surveillance". The publicly available KV data report shows aggregated information on completeness of the vaccinations received and compliance with the recommended vaccination schedule [9]. Analyses for birth cohort 2011 reported that a large proportion of children in Germany was vaccinated too late against pneumococci. Only 40–50% of children received the 3rd dose by the age of 6 months and the booster dose was merely administered to only 30–40% of children by the age of 15 months. By 24 MoA, full PCV immunization was achieved in approximately 75% of children [5]. Beginning in 2020, the data collected on the vaccination status from school entrance examinations and vaccination-related claims data of the KV's will be reported in an annual overall presentation [9]. Based on KV's claims data, the first published report stated a full PCV immunization status after 24 months in 69.3% of children born in 2016. Among the children attending a school entry examination in 2018, 82.1% were fully vaccinated against pneumococci [10].

However, it is important to consider specific limitations of the above-mentioned data sources. The immunization status collected during the school entry examination is recorded for children of school entrance age [9]. Therefore, the vaccination status of children born after 2013 is not yet completely included in the latest surveillance data and, therefore, it is currently not possible to analyze a potential effect of the modified STIKO recommendations. Furthermore, the timeliness of the PCV has not been assessed as the primary focus of analysis is the completeness of immunization against pneumococci. The KV claims data contain information on individual vaccinations administered and the time of vaccination for each insured person. Nevertheless, a longitudinal analysis of these data is only possible for individuals who do not change their place of residence to another KV region during the study period since the individual insurance data cannot be traced across KV regions [9]. Neither the KV's claims data, nor the vaccination rates being collected as part of the school entry examination differentiate between premature and mature born children. Without considering the differentiation, both evaluations might be subject to biases due to the different vaccination recommendations for mature and premature infants. Accordingly, no conclusions can be drawn about the vaccination rate against pneumococci and adherence to the STIKO recommended vaccination schedule in the subpopulation of mature born infants.

The study aim was to generate real-world evidence on the change in vaccination rates, series completeness, and timeliness for vaccination against pneumococci in mature infants before and after the change of the STIKO recommendation and to compare the results to the hexavalent vaccination (HEXA; vaccination against polio, diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b and hepatitis B) as a reference continuing with a 3+1 schedule during the study period.

2. Materials and Methods

2.1. Data source

A retrospective claims database analysis was conducted using claims from the "Institut für angewandte Gesundheitsforschung Berlin" (InGef) Research Database. The InGef database consists of approximately 8 million covered lives and includes the healthcare resource utilization and costs of services in an anonymized case-by-case individual format. For scientific purposes, a sample of the InGef database is available which includes more than 4 million covered lives and is representative in terms of age and gender for the German population. The InGef Research Database comprises healthcare claims data from about 60 different health insurances covering more than half of the overall number of Statutory Health Insurances (SHI) in Germany. Furthermore, the sample represents approximately 4.8% of the German population [11] and about 5.5% of the SHI population [12] as of 2018 and has proven to have good external validity to the German population in terms of morbidity, mortality, and drug use [13]. Data contributing to the InGef database are stored at a specialized data center owned by SHIs providing data warehouse services. In the data center (acting as a trust center), data with respect to individual insured members, health care providers (e.g. physicians, practices, hospitals, pharmacies), and the respective SHI are anonymized. All data were analyzed by InGef staff based on the study protocol and only aggregated data were provided.

2.2. Patient identification

Subjects of the study were mature newborns available within the InGef Research Database who were born between 01 January 2013 and 31 December 2013 (reference cohort) and 01 January 2016 to 31 December 2016 (observation cohort). Within both cohorts, premature newborns were excluded using the following diagnoses codes of the International Classification of Diseases, 10th Revision, German Modification (ICD-10-GM):

- P07.2: newborns with a gestational age of <28 completed weeks of pregnancy
- P07.3: newborns with a gestational age of ≥28, but < 37 completed weeks of pregnancy.

In Germany, outpatient procedures are billed using the German physician fee schedule (EBM). For vaccinations, a different EBM code is assigned to each vaccine/disease protected against. Data sets of infants showing incomplete information regarding the vaccination date based on documented EBM codes were treated as unvaccinated but still eligible and remained in the study population as part of the denominator when assessing vaccination rates and immunization status. The identified individuals were followed-up for individual 24 months and had to be continuously insured until the follow-up was completed.

Fig. 1 illustrates the study design and the data availability periods for each birth cohort.

2.3. Study outcomes

Both birth cohorts were analyzed in terms of PCV rate, completeness, and timeliness of each administered dose according to the respective STIKO recommendation [14]. For all mature infants

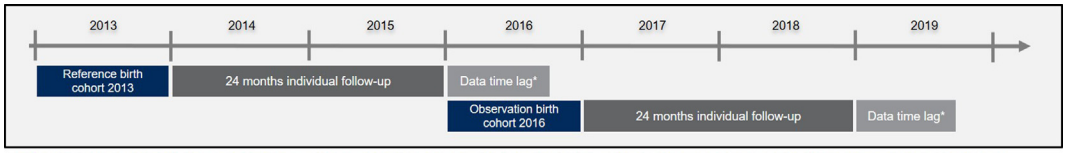

Fig. 1. Study Design and Study Period.

born in 2013, the outcome assessment was based on the respective STIKO recommendation of a 3+1 PCV schedule while outcomes for the birth cohort 2016 were analyzed considering the changed 2+1 schedule.

In order to assess the implications of the different STIKO recommendations for PCV applicable in 2013 and 2016, the HEXA vaccination was analyzed as a reference vaccine. The HEXA vaccination scheme remained unchanged with a 3+1 vaccination schedule throughout the study period [15].

Vaccinations were identified by assessing documentation of vaccination EBM codes (PCV: 89118* or 98120*, HEXA: 89600*) recorded in the outpatient setting during an individual follow-up period of 24 months beginning at birth. Due to the EBM coding, different brands of vaccines for PCV, for instance the 10-valent or 13-valent pneumococcal vaccine, cannot be distinguished.

All infants identified as vaccinated were stratified by the individually applied number of vaccine administrations according to the definitions in Table 1 for incomplete, basic, and full immunization:

2.3.1. Vaccination rate

Vaccination rates based on the total number of identified mature infants within the reference and observation cohorts 2013 and 2016 (including infants without any vaccination) were calculated for all identified individuals with at least one PCV and/or HEXA vaccination. Additionally, the percentage of vaccinated infants in the respective birth cohorts was determined for each PCV and HEXA dose (0, 1, 2, 3, 4, ≥5 doses) administered during the individual observation period.

2.3.2. Immunization status – Completeness

The percentage of mature infants in both birth cohorts 2013 and 2016 achieving no immunization, an incomplete immunization, basic immunization, and full immunization status for PCV and HEXA was assessed considering the number of doses received during the 24 months of individual follow-up by applying the definitions displayed in Table 1.

2.3.3. Compliance to vaccination – Timeliness

To analyze the timeliness of vaccine administration recommended by the STIKO, the age at vaccination determined by date of birth and date of vaccination was taken into consideration. All administered vaccinations during 24 months of follow-up were analyzed by taking the MoA into account when the 1st, 2nd, 3rd, 4th, or ≥5 doses were applied. Within each MoA, the percentage of those mature children who received respective vaccination doses was calculated based on the number of vaccinated infants per MoA and per dose. Based on the number of infants who were vaccinated with the appropriate dose, the number and percentage of children who have been vaccinated on schedule were calculated per dose, meaning all children receiving the vaccination exactly within the recommended MoA. Children receiving the vaccination before or after the recommended MoA were classified as not vaccinated on schedule; no tolerance range was provided according to STIKO.

Fig. 2 summarizes the analysis of outcome variables and the comparisons of PCV with HEXA vaccination as well as the comparisons between the reference cohort 2013 and the observation cohort 2016.

2.4. Statistical analysis

As only aggregated results for vaccination rates were assessed, vaccination rates between 2013 and 2016 were descriptively compared for both PCV and HEXA vaccinations by taking respective 95% confidence intervals (CI) derived as Clopper-Pearson-CI for binomial distributed data with unknown probability into account. Respective vaccination rates without an overlap between the CIs were considered to differ significantly ($p<0.05$).

3. Results

3.1. Patient population

In the reference cohort 2013, 32,978 mature infants with 24 months of follow-up were identified. The observation cohort 2016 consisted of 50,844 mature born infants. While in 2013 93.1% of births resulted in mature newborns, this proportion increased to 95.1% of births in 2016. The gender distribution of mature born infants was similar within both birth cohorts with 51.1% (2013) and 51.3% male newborns (2016), respectively.

Table 1
Definitions for Incomplete, Basic, and Full Immunization for PCV and HEXA Vaccination.

	Reference cohort 2013		Observation cohort 2016	
	PCV	HEXA	PCV	HEXA
No vaccination				
Incomplete basic immunization	1st or 2nd vaccination only	1st or 2nd vaccination only	1st vaccination only	1st or 2nd vaccination only
Basic immunization	1st, 2nd, and 3rd vaccination	1st, 2nd, and 3rd vaccination	1st and 2nd vaccination	1st, 2nd, and 3rd vaccination
Full immunization	1st, 2nd, 3rd, and ≥ 4 vaccinations	1st, 2nd, 3rd, and ≥ 4 vaccinations	1st, 2nd, and ≥ 3 vaccinations	1st, 2nd, 3rd, and ≥ 4 vaccinations

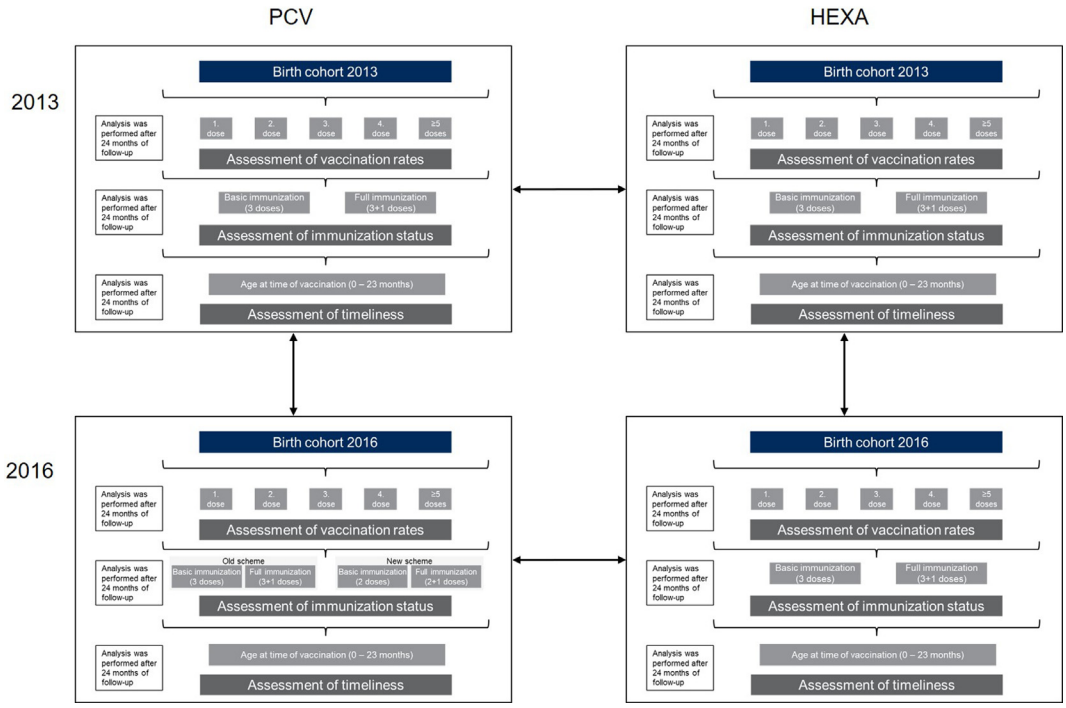

Fig. 2. Outcome Analyses and Comparisons of the Study Cohorts.

3.2. Vaccination rate

In comparison to 2013 (3+1 scheme), the overall PCV rate (at least one dose) of mature born infants (91.2% vs 90.9%) did not change in 2016 (2+1 scheme). Compared to PCV, the overall HEXA vaccination rate increased significantly ($p<0.05$) from 88.9% to 91.6%.

3.3. Immunization status - Completeness

After 24 months of individual follow-up, the proportion of mature infants achieving the full immunization status of PCV increased significantly ($p<0.05$) from 68.3% (3+1 scheme) in 2013 to 75.6% (including 71.7% of children with PCV according to a 2 +1 scheme and 3.9% of infants vaccinated according to a 3+1 scheme) in 2016 (see Fig. 3). Likewise, the vaccination rates of full HEXA vaccination (3+1 scheme in 2013 and 2016) increased significantly ($p<0.05$) for mature newborns (69.1% vs 72.9%) in 2016.

3.4. Compliance to vaccination schedule – Timeliness

Fig. 4 illustrates the percentage of mature infants receiving PCV (1^{st}, 2^{nd}, 3^{rd}, 4^{th} dose) stratified by MoA at administration (0–23 MoA) within 24 months of follow-up for the cohorts 2013 (see panel (A)) and 2016 (see panel (B)). The percentage of mature newborns that were vaccinated on schedule according to the STIKO recommendation is highlighted for each dose. The timeliness of the first PCV dose (51.1% vs 44.2%) and the basic immunization (3^{rd} dose 2013 and 2^{nd} dose 2016) (31.3% vs 26.7%) increased significantly ($p<0.05$) in 2016 compared to 2013. The proportion of children receiving the booster PCV on time remained unchanged (45.1% vs 46.3%) when comparing mature born infants in 2013 and 2016.

The timeliness for HEXA vaccination in 2013 (see panel (A)) and 2016 (see panel (B)) is depicted in Fig. 5. The proportion of infants receiving the first three HEXA doses on time according to the STIKO recommendation increased significantly ($p<0.05$) in 2016 compared to 2013 (1^{st} dose: 51.4% vs 45.6%, 2^{nd} dose: 43.3% vs 39.3%, 3^{rd} dose: 29.5% vs 27.6%). Also, the proportion of infants receiving the booster HEXA vaccination on time rose to 50.0% in mature born infants from 2016 (47.8% in 2013), but this difference was not statistically significant.

Fig. 6 shows that about 9% of children in both cohorts remained unvaccinated, that the booster PCV dose was often missing (25.1% in 2013 and 16.8% in 2016), and that overall, children were vaccinated too late against pneumococci. A stratification of the administration of the 3^{rd} PCV dose in 2016 by 0–10 MoA and 11–23 MoA demonstrates deviations from the STIKO's recommended vaccination scheme. About 5% of mature infants received their third dose (booster dose according to the 2+1 schedule) at a younger age (0–10 MoA) than recommended by the STIKO (compared to 0.7% in 2013 with a booster administration (4^{th} dose) until the age of 11 months). Around 4% of mature infants born in 2016 received a 4^{th} dose after the age of 10 months which would indicate a 3+1 vaccination schedule.

In contrast, the comparison of the cumulative HEXA rates after 24 months of follow-up (no stratification applied as the HEXA vaccination schedule remained unchanged) indicated only a slight difference for each HEXA dose between the time of administration in mature infants 2013 and 2016 (see Fig. 7).

4. Discussion

This retrospective claims database analysis provides insights into the policy change's impact regarding the vaccination scheme of the pneumococcal conjugate vaccine and the respective immunization status of mature newborns in connection with the corresponding STIKO recommendation. This study adds valuable insights to the already published data from the KV surveillance by analyzing data at the individual patient level as well as longitudinal vaccination pathways including timeliness of vaccination in mature born infants in Germany. Within the InGef Research Database, 32,978 and 50,844 mature infants with 24 months of follow-up were identified in the reference cohort 2013 and observation

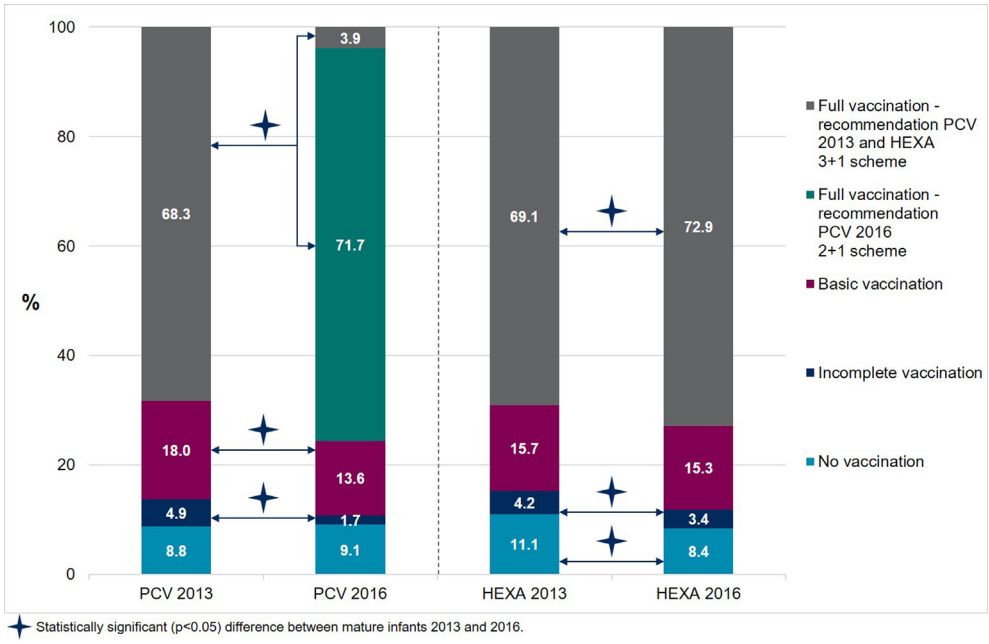

Fig. 3. Immunization Status for PCV and HEXA Vaccination After 24 Months of Follow-up – Mature Infants 2013 and 2016.

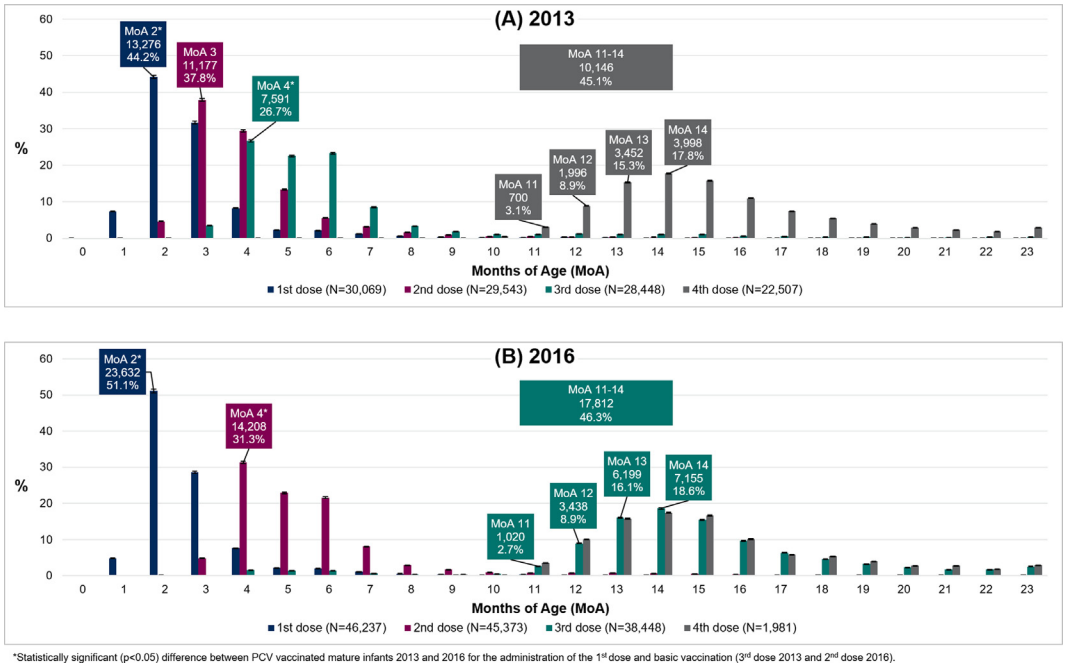

Fig. 4. Timeliness of PCV After 24 Months of Follow-up – Mature Infants 2013 and 2016.

cohort 2016, respectively, corresponding to a proportion of mature newborns of approximately 93% and 95%. Own calculations based on hospital birth statistics revealed a proportion of mature births (i.e. ≥37 weeks of gestation) of approximately 91% in 2013 and 2016 for Germany [16,17], which is a slightly lower proportion of mature infants than that identified in the present study.

The pneumococcal conjugate immunization in mature infants was recommended as a 3+1 vaccination cycle until August 2015, where the STIKO changed the recommended PCV schedule for full immunization to a 2+1 scheme for mature newborns. The STIKO's rationale for adjusting the PCV schedule included that a reduction of the recommended dosages could lead to a higher acceptance for the vaccination and thus to higher vaccination rates [5]. The present study did not find an increased number of mature infants receiving at least one dose of pneumococcal conjugate vaccine (about 91% in both birth cohorts) and a corresponding substantial share of newborns (about 9% in both cohorts) remained unvaccinated. However, a significant ($p<0.05$) increase in the proportion of mature infants with full pneumococcal conjugate immunization status was identified when comparing birth cohorts 2013 and 2016 (68.3% vs 75.6%). Although the 2+1 schedule was implemented in most cases, the data indicate that some infants born in 2016 were still vaccinated according to a 3+1 schedule. About 5% of mature infants received their 3rd pneumococcal conjugate vaccine dose

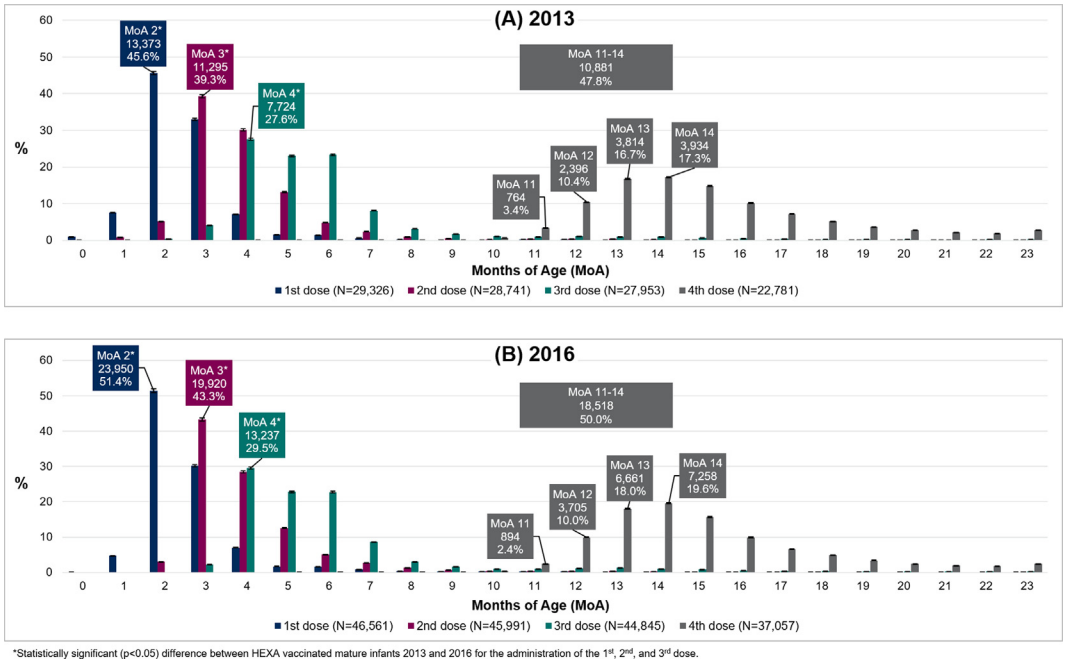

Fig. 5. Timeliness of HEXA Vaccination After 24 Months of Follow-up – Mature Infants 2013 and 2016.

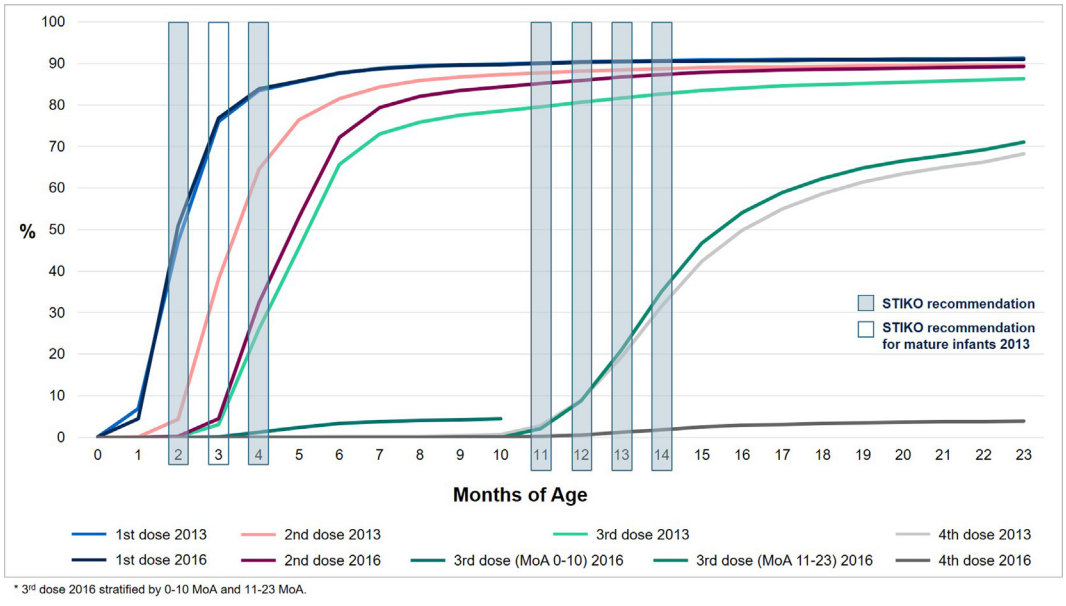

Fig. 6. Cumulative PCV Rates of Mature Infants 2013 and 2016 Until 23 Months of Age*

(recommended booster dose for full immunization) before the age of 11 months and about 4% of the mature newborns in 2016 received a 4th pneumococcal conjugate vaccine dose. The reason why a notable proportion of children were not vaccinated according to the recommended 2+1 schedule cannot be inferred from the underlying data source. Potential influencing factors related to a deviation from the STIKO recommendation could include that the infant's immunization history or annually changing recommendations might be unknown to the treating physician. Further, the PCV administration according to a 3+1 schedule might be associated with an increased protection against potential IPD and thus preferred by some doctors.

While the identified positive trend in full pneumococcal conjugate immunization could be linked to the change in the STIKO recommendation, it cannot be ruled out that other (potentially latent) factors could also have influenced this trend. Likewise, the results regarding HEXA immunization showed that, without any changes of the vaccination schedule, significantly ($p<0.05$) more mature newborns received at least one HEXA vaccination (91.6% vs 88.9%) as well as full HEXA immunization (72.9% vs 69.1%) in 2016.

The comparison of the present findings to the nationwide surveillance on vaccination status including all outpatient vaccinated children covered by the SHI across all federal states in Germany (also referred to as "KV data") revealed lower full PCV rates: Based on

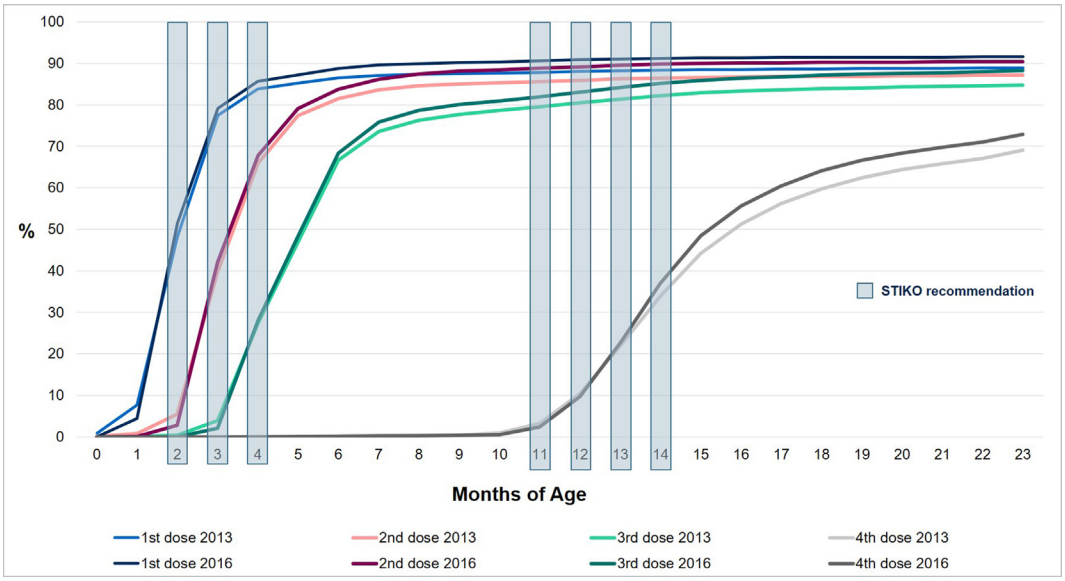

Fig. 7. Cumulative HEXA Vaccination Rates of Mature Infants 2013 and 2016 Until 23 Months of Age.

vaccination-related claims data, the KV data reports that 69.3% of children born in 2016 were fully vaccinated against pneumococci after 24 months of follow-up. Of the fully-vaccinated children, 63.4% were vaccinated according to the 2+1 scheme recommended since August 2015 and 5.9% received four vaccine doses instead. This analysis was not stratified to account for different vaccination schedules for mature and premature born infants in the previous birth cohorts 2008–2015, the rate of completely vaccinated children ranged from 66% to 71%. For HEXA, the KV data indicated that 78% of all children in birth cohort 2016 completed their vaccination series in the first 24 months of life which represents a higher rate than reported in our study. Of those children who completed their vaccination series in the first 24 months of life, 75% were vaccinated according to the 3+1 schedule recommended and 3% received solely three vaccine doses instead. In contrast to our study, a decreasing trend in full HEXA vaccination rates is reported in the vaccination-related claims data [10].

Among the children attending a school entry examination and presented a vaccination certificate in 2018, 82.1% were fully vaccinated against pneumococci. Since survey year 2011, the proportion of children with full pneumococcal conjugate immunization rose rapidly and reached 83–85% from 2013 onwards, likely because they were among the first children born after the introduction of the vaccination recommendation in 2006. For HEXA, more than 90% of children attending a school entry examination in 2018 showed a full immunization status regarding polio, diphtheria, tetanus, pertussis, and *Haemophilus influenzae* type b, while the uptake of the hepatitis B vaccination accounted for 87.2%. In contrast to PCV, a decreasing trend in full HEXA vaccination rates is reported for vaccination quotas obtained during the school entry examination [10]. In general, the described vaccination rates collected as part of the school entry examination were higher in comparison to the presented PCV and HEXA vaccination rates of birth cohorts 2013 and 2016. While the vaccination rates identified in the present study relied on billed EBM codes for vaccinations, vaccination rates determined during the school entrance examination could only be calculated for children presenting a vaccination certificate. This might lead to an overestimation of the vaccination rates as children who received vaccinations could be more likely to present a vaccination certificate [9,18]. On the other hand, the school entrance examination could record catch-up vaccinations in children with underlying chronic diseases that were carried out after the recommended vaccination timeframe since the examination is undertaken in children aged five to seven years, leading to a higher reported vaccination rate in comparison to KV's vaccination-related claims data with 24 months of follow-up and the results presented here [9,10].

Generally, a slightly positive trend in vaccination rates on the national level is noticeable. The vaccination rates of 1st and 2nd measles vaccinations have continuously increased in the birth cohorts of 2008 to 2017. Overall, there has been a slight increase in the combined vaccination against measles, mumps, and rubella over the past 10 years. A similar positive trend can be seen for varicella and meningococci [10]. Accordingly, the reported increase in PCV rates might be attributable to the overall positive trend in vaccination rather than the STIKO recommendation change. In contrast, an increase in vaccine hesitation has been observed in Western countries during the last years due to complacency, convenience, and mistrust [19]. Parental attitudes and predictors influencing infants and adolescent vaccine updates, completion of the vaccination schedule, and compliance to recommendations have been intensively studied by Theeten and colleagues in Belgium. It was reported that individual (age, school career) and family-level characteristics (family income, parental educational level or screening behavior by the mother) are significantly associated with vaccine uptake [20]. However, the assessment of the influence of these factors was not part of this study.

Beside the public recommendations by the STIKO, physicians also influence the vaccination rates and the timeliness of vaccinations. In Germany, physicians have the responsibility to inform parents about the vaccination recommendations and to monitor the vaccination status of the infants [21]. Furthermore, regular check-ups for infants and children are in place, covering ten different examinations beginning with birth until the age of six years. Generally, regular check-ups and vaccinations are independent from each other. However, the defined periods for the check-ups do occasionally overlap with the recommended timeframe for vaccinations [22]. Depending on the physician, it might be possible that PCV and HEXA vaccinations are administered simultaneously and have influenced the date of the vaccinations. As we did not investigate the compliance with the recommended time frame for regular check-ups in the study populations, it is not possible

to assess any correlations between, or draw any conclusions regarding the examinations and the vaccination dates.

In recent years, vaccination campaigns on state and federal state level, such as the Bavarian Vaccination Week, which is conducted every two years since 2009 [23] and the nationwide campaign "Deutschland sucht den Impfpass" [24] of the German Federal Centre for Health Education (Bundeszentrale für Gesundheitliche Aufklärung – BzgA) initiated in 2012 might also have impacted vaccination rates in Germany. Even though the vaccination campaigns were not specifically targeting PCV, they might still be associated with an increasing awareness of the need for vaccinations in general and thus also raise vaccination rates against pneumococci.

5. Strength and Limitations

In general, claims data are an appropriate and comprehensive tool for analyzing epidemiological measures, health care utilization, and health care costs as these data are recorded independently of any study purposes or clinical research recruiting participants. For all included newborns, the use of SHI claims data allows the assessment of vaccinations recommended by the STIKO for each age group. With the help of the patient-individual pseudonym, the completeness of the vaccinations received and the adherence to the recommended vaccination schedule could be derived for each newborn separately. Accordingly, individual vaccination pathways could be traced, with both cross-sectional evaluations (e.g. vaccination rates of the birth cohorts in 2013 and 2016 at 23 MoA) and longitudinal analyses and comparisons (e.g. vaccination rate development within a birth cohort with increasing age).

Nevertheless, claims data from the SHI are subject to some limitations which must be considered when interpreting the results of claims data analysis. As the data analyzed in this study derive from SHI only, the German private health insurance sector was not included. Accordingly, newborns who are insured with a German private health insurance were not included in the study population. As approximately 88% of the German population, corresponding to about 73 million individuals, is insured in the SHI [11,12], only a small proportion of newborns should accordingly be insured in a private health insurance. Further, the study population consisted only of newborns who had complete data in terms of date of birth and the required individual follow-up period of 24 months. Newborns who were not continuously insured during the follow-up period due to sickness fund switch or death were not included in the study. As data sets with incomplete vaccination dates were treated as unvaccinated but still eligible and remained in the underlying study population, selection bias is unlikely. Nevertheless, it is necessary to consider that especially children with chronic conditions, who often lack vaccinations or who experience a delay of vaccinations, could have been excluded from the study due to death in the follow-up period. Furthermore, as both sickness fund switch and lack or delay of vaccination might be associated with socioeconomic status, which is not available in this data source, biases due to unmeasured confounding are possible. Another limitation is that German claims data do not contain detailed information on drugs or vaccines that have been applied in the inpatient setting. Therefore, the analysis might underestimate the vaccinations which were administered during inpatient stays. Finally, SHI claims data are collected primarily for reimbursement purposes. Therefore, the reasons why children did not receive an immunization or received an incomplete vaccination series are unknown, as the physicians' intention of treatment, potential intolerances to particular ingredients in vaccines, and parents' attitude towards vaccination are not available in claims data. Accordingly, the study was not able to clarify why vaccinations are not administered on schedule.

6. Conclusions

There is no clear evidence that the reduction of the vaccination schedule for PCV induced a higher acceptance of pneumococcal conjugate vaccines. A relevant share of mature infants remained unvaccinated with pneumococcal conjugate vaccines (2013 and 2016: both approximately 9%), while the proportion of mature infants without HEXA immunization decreased slightly (11% vs 8%). The rates of mature infants who were fully-vaccinated increased for PCV (68% vs 76%) as well as for HEXA vaccination (69% vs 73%) from 2013 to 2016. The proportion of children receiving the PCV or HEXA booster vaccination on time showed no significant change (PCV: 45% vs 46%, HEXA: 48% vs 50%) when comparing mature born infants in 2013 and 2016. Some mature born infants in 2016 still received four PCV doses, indicating that they have been vaccinated against pneumococci according to the old STIKO recommendation. Overall, even with a reduction of recommended doses, a substantial proportion of mature infants still did not receive a full PCV immunization in a timely manner. Further discussions with medical experts on underlying reasons for deviations from the recommended vaccination schedule and on the temporal relationship between regular check-ups and vaccinations are needed to uncover the background for the presented findings. Moreover, the results of this study suggest policymakers should consider supportive measures to increase the vaccination rates. The electronic vaccination certificate, which will be available from 2022 onwards as part of the electronic patient record [25], and reminder systems integrated into physicians' practice software could positively influence the vaccination up-take. Future research should aim at consistent monitoring of data recorded in the electronic vaccination certificate to provide insights into the development of vaccination rates, compliance, and timeliness of vaccination in the coming years.

Author's contribution

M. Laurenz and C. von Eiff are employees of Pfizer Pharma GmbH, Germany. K. Schley is an employee of Pfizer Deutschland GmbH, Germany. K. Borchert, K. Seidel, and C. Jacob are employed by Xcenda GmbH which received consulting fees for the execution of the study and manuscript preparation from Pfizer Pharma GmbH, Germany.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Modul 10

Vaccination rates and adherence in premature infants before and after pneumococcal conjugate vaccine schedule change for term infants – A claims database analysis in Germany

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Vaccination rates and adherence in premature infants before and after pneumococcal conjugate vaccine schedule change for term infants – A claims database analysis in Germany

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ABSTRACT

Background: In 2015, the German Standing Committee on Vaccination (STIKO) changed the pneumococcal conjugate vaccination (PCV) schedule for mature infants from a 3+1 scheme (2, 3, 4, and 11–14 months of age) to a 2+1 scheme (2, 4, and 11–14 months of age). For premature infants, the 3+1 scheme remained. The aim of this study was to assess vaccination rates, completeness, and timeliness for PCV in premature infants before and after the modified recommendation.
Methods: A retrospective claims data analysis using the "Institut für angewandte Gesundheitsforschung Berlin" Research Database was conducted. Premature infants born in 2013 and 2016 with an individual follow-up of 24 months were included. Hexavalent combination (HEXA) vaccination with a consistent 3 +1 recommendation for mature and premature infants was analyzed as reference vaccination.
Results: After 24 months, the PCV rate for at least one dose remained stable in premature newborns of 2016 compared to 2013, while the HEXA vaccination rate increased slightly. However, a significant decrease of a completed PCV schedule (4 doses) in premature infants was noted, whereas the completeness of HEXA vaccination did not change. The timeliness of PCV in premature newborns increased for the first and the booster PCV, while the timeliness of HEXA immunization did not change from 2013 to 2016.
Conclusion: Although STIKO still recommends a 3+1 PCV schedule for premature infants in Germany, premature infants were vaccinated according to the changed recommendations for mature born infants. A substantial share of premature infants remained unvaccinated, and their vaccinations were often delayed.

1. Introduction

In Germany, 8% to 9% of infants are born prematurely each year [1]. Premature births are known to lead to impaired immunity, a reduced transplacental transfer of antibodies, a decreased immune response to vaccinations due to an immature immune system, and therefore, a heightened risk of infectious diseases and infection-related mortality [2–4]. For instance, Kent et al. observed that the risk of invasive pneumococcal disease (IPD) is significantly higher in premature infants compared to infants born at term (49 vs 17 per 100,000 infants; incidence rate ratio: 2.87; p<0.001). They concluded that the recommendation to reduce the United Kingdom 2+1 pneumococcal immunization schedule (two priming doses plus a booster) to a 1+1 schedule (single priming dose plus a booster) will need careful monitoring, especially in premature infants, who may be disproportionately affected by this change [2].

In Germany, the first recommendation for pneumococcal conjugate vaccination (PCV) was introduced in July 2001 by the German Standing Committee on Vaccination (STIKO), targeting infants at

Abbreviations: CI, Confidence Interval; EBM, German physician fee schedule (Einheitlicher Bewertungsmaßstab); HEXA, Hexavalent; ICD-10-GM, International Classification of Diseases, 10th Revision, German Modification; InGef, Institute for Applied Health Research Berlin (Institute für angewandte Gesundheitsforschung Berlin); IPD, Invasive Pneumococcal Disease; MoA, Months of Age; PCV, Pneumococcal Conjugate Vaccination; SHI, Statutory Health Insurance; STIKO, Standing Committee on Vaccination (Ständige Impfkommission).

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increased risk for IPD including premature infants born before 38 completed weeks of gestation and infants with a birth weight of <2,500 g [5]. In July 2006, the STIKO recommended the PCV for all children up to the age of 24 months in a 3+1 schedule with 4 doses administered at 2, 3, 4, and 11–14 months of age (MoA) [6]. Following the STIKO recommendation, vaccinations and respective physicians' consultations are reimbursed by the Statutory Health Insurance (SHI) in Germany with no co-payments for the patients. The vaccinations are administered routinely in outpatient practices or, under special circumstances, during hospitalizations.

Comparing premature birth cohorts of 2000 and 2007 in Germany, the IPD rate decreased from 26.1 to 16.7 per 100,000 following the introduction of the 7-valent pneumococcal vaccine. A similar reduction was observed in mature infants (from 15.0 to 8.5 per 100,000 infants) [7]. Higher valent vaccines were introduced in April 2009 (PCV10) and December 2009 (PCV13) in the German market. Consequently, reported IPD cases decreased from 11.1 per 100,000 in 2003–2006 to 5.9 per 100,000 in 2017–2018 among children under two years of age [8]. Unfortunately, no data exist regarding the IPD incidence after the introduction of PCV10 and PCV13 stratified by mature and premature newborns for Germany. After the 13-valent PCV was introduced in the United Kingdom, the overall IPD incidence was observed to be 19 per 100,000 infants and significantly higher in premature infants compared to mature born infants (49 vs 17 per 100,000 infants) between 2013 and 2016. Premature children born before the 28th week of gestation had an increased incidence rate of 150 per 100,000 infants [2].

In August 2015, the STIKO changed the PCV scheme for mature infants from a 3+1 to a 2+1 schedule (3 doses administered at 2, 4, and 11–14 MoA). For premature infants, the 3+1 scheme remained [6]. Yet, evidence on vaccination rate, completeness, and timeliness of PCV administration in Germany are scarce. Two sources, the school entry examination [9] and the claims data analysis by the Statutory Health Insurance (SHI) Physician Association [10], provide data on PCV status. However, both do not distinguish between mature and premature born infants and the respective differences in vaccination schedules. Accordingly, no conclusions can be drawn about the PCV rate and adherence to the vaccination schedule recommended by the STIKO in the subpopulation of premature newborns.

This analysis was part of a study to assess the vaccination rates, compliance, and adherence before and after the change of the PCV recommendation in 2015 for both, mature and premature born infants. Laurenz et al report the results for the mature born infants of birth cohorts 2013 and 2016 [11].

The aim of this analysis was to generate real world evidence on the evolution of vaccination rates, completeness, and timeliness for PCV in premature infants and to compare the results to the hexavalent combination (HEXA; vaccination against polio, diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b, and hepatitis B) vaccination as a reference for the premature birth cohorts 2013 and 2016.

2. Materials and methods

2.1. Data source

A retrospective claims database analysis was conducted using anonymized claims from the "Institut für angewandte Gesundheitsforschung Berlin" (InGef) Research Database. The InGef Research Database comprises healthcare claims data of more than 4 million individuals and is representative in terms of age and gender for the German population. It contains data from about 60 different health insurances covering more than half of the overall number of SHIs in Germany. For a detailed database description please refer to the publication on PCV in mature infants recently published by Laurenz et al. [11].

2.2. Patient identification

Premature children in the InGef Research Database born between 01 January 2013 and 31 December 2013 (reference cohort) and 01 January 2016 to 31 December 2016 (observation cohort) with the following International Classification of Diseases, 10th Revision, German Modification (ICD-10-GM) diagnoses codes

- P07.2: newborns with a gestational age of <28 completed weeks of pregnancy
- P07.3: newborns with a gestational age of ≥28, but <37 completed weeks of pregnancy

were identified.

The identified children had to be continuously insured until an individual follow-up of 24 months was completed.

2.3. Study outcomes

Both birth cohorts were analyzed in terms of PCV rate, completeness, and timeliness of each administered dose according to the STIKO recommendation [12].

In order to assess the implications of the different STIKO recommendations present in premature and mature infants, the HEXA vaccination was analyzed as a reference vaccine with an unchanged 3+1 vaccination schedule throughout the study period [13,14].

Outpatient procedures, like the administration of vaccines, are billed using the Physician Fee Schedule (EBM) in Germany. Vaccinations were identified by assessing documentation of EBM codes for vaccination (PCV: 89118* or 98120*, HEXA vaccination: 89600*) recorded in the outpatient setting during the individual follow-up period of 24 months beginning at birth. Infants with incomplete information regarding the vaccination date based on documented EBM codes remained in the study population as part of the denominator when assessing vaccination rates and immunization status. However, they were counted as unvaccinated.

2.3.1. Vaccination rate

Vaccination rates were calculated for all identified individuals with at least one PCV and/or HEXA vaccination based on the total number of premature newborns within the reference and observation cohort 2013 and 2016.

2.3.2. Immunization status – Completeness

The immunization status of PCV and HEXA vaccination in premature infants in 2013 and 2016 was assessed by applying the following definitions:

- Incomplete basic immunization: 1st or 2nd vaccination
- Basic immunization: 1st, 2nd, and 3rd vaccination
- Booster immunization: 4th vaccination
- Full immunization: 1st, 2nd, 3rd [basic immunization] and 4 or more vaccinations [full immunization].

2.3.3. Compliance to vaccination – Timeliness

The age at vaccination determined by date of birth and date of vaccination was considered to analyze the timeliness of vaccine administration recommended by the STIKO. The number and percentage of premature children being vaccinated on track within the recommended MoA were calculated per dose. Infants being vaccinated before or after the recommended MoA for the respec-

tive dose were classified as not vaccinated on schedule. According to STIKO, no tolerance range in MoA was provided.

2.4. Statistical analysis

For these descriptive analyses, we compared whether the vaccination rates in 2013 and 2016 differed between the birth cohorts and between the PCV and HEXA vaccinations by considering respective 95% Clopper-Pearson confidence intervals (CI) for binomial distributed data with unknown probability. CIs of respective vaccination rates without an overlap were considered to differ significantly ($p < 0.05$).

3. Results

3.1. Patient population

In the reference cohort 2013, 2,448 premature newborns with 24 months of follow-up were identified. The observation cohort 2016 consisted of 2,610 premature born infants. While in 2013 approximately 7% of pregnancies resulted in premature births, this applied to approximately 5% in 2016. Slightly more male infants (55% in 2016 and 56% in 2013) were born prematurely.

3.2. Vaccination rate

Compared to 2013, the overall PCV rate (at least one dose) of premature born infants did not change in 2016 (both approximately 94%). Opposing to PCV, the overall HEXA vaccination rate increased significantly ($p < 0.05$) from 92% to 95%.

3.3. Immunization status – Completeness

After 24 months of follow-up, approximately 65% of premature newborns in 2013 received the full PCV immunization (4 doses), while only 41% of premature born infants in 2016 were fully vaccinated against pneumococci (significant difference at $p < 0.05$). Differently, the full immunization with HEXA vaccination in premature infants experienced no significant changes over time (see Fig. 1).

3.4. Compliance to vaccination schedule – Timeliness

The proportion of premature infants receiving the first PCV dose on time according to the STIKO recommendation increased significantly ($p < 0.05$) in 2016 compared to 2013 (45% vs 41%), whereas the second (26% vs 35%) and third dose (19% vs 25%) were administered significantly ($p < 0.05$) more frequently on time in premature infants in 2013. The proportion of children receiving the booster PCV (4^{th} dose) on time rose numerically when comparing premature newborns in 2013 and 2016 (44% vs 48%) without reaching statistical significance (see Fig. 2).

The proportion of premature infants receiving the first HEXA vaccination dose on time increased significantly ($p < 0.05$) in 2016 compared to 2013 (46% vs 41%). The administration of the second (39% vs 36%) and third HEXA vaccination dose (28% vs 26%) was more frequently on time in premature infants born in 2016, but this difference was not statistically significant. There was no significant difference in the proportion of infants with booster HEXA vaccination. In both cohorts 2013 and 2016, about 47% of premature children received the 4^{th} HEXA vaccination dose on time according to the STIKO recommendation (see Fig. 3).

The cumulative PCV rates in Fig. 4 indicate that about 6% of premature children in both cohorts remained unvaccinated, that the booster PCV dose was often missing (31% in 2013 and 57% in 2016), and that overall, premature infants were vaccinated too late against pneumococci. A stratification of the administration of the 3^{rd} PCV dose in 2016 by 0–10 MoA and 11–23 MoA illustrates that about 34% of premature infants received their supposed basic vaccination (3^{rd} PCV dose) at the age of ≥11 months (compared to about 14% in 2013 with a basic immunization at the age of ≥11 months).

Conversely, the comparison of the cumulative HEXA vaccination rates after 24 months of follow-up indicated only a slight, not significant difference for each HEXA vaccination dose between the

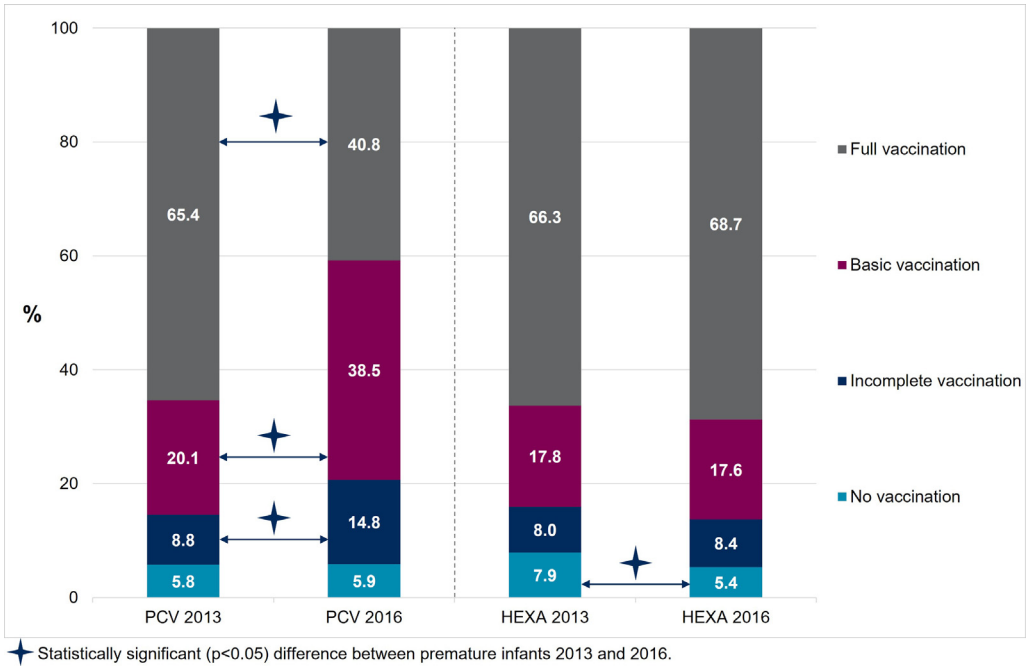


Fig. 1. Immunization status for PCV and HEXA vaccination until 23 months of age – premature infants 2013 and 2016.

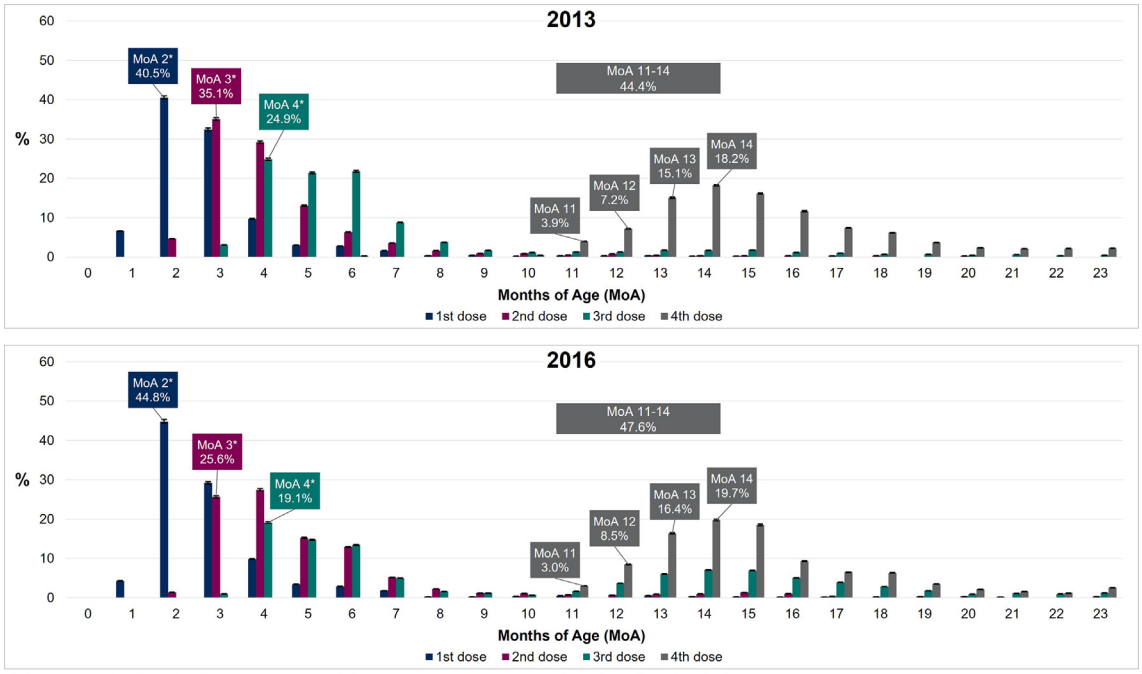


Fig. 2. Timeliness of PCV until 23 months of age – premature infants 2013 and 2016.

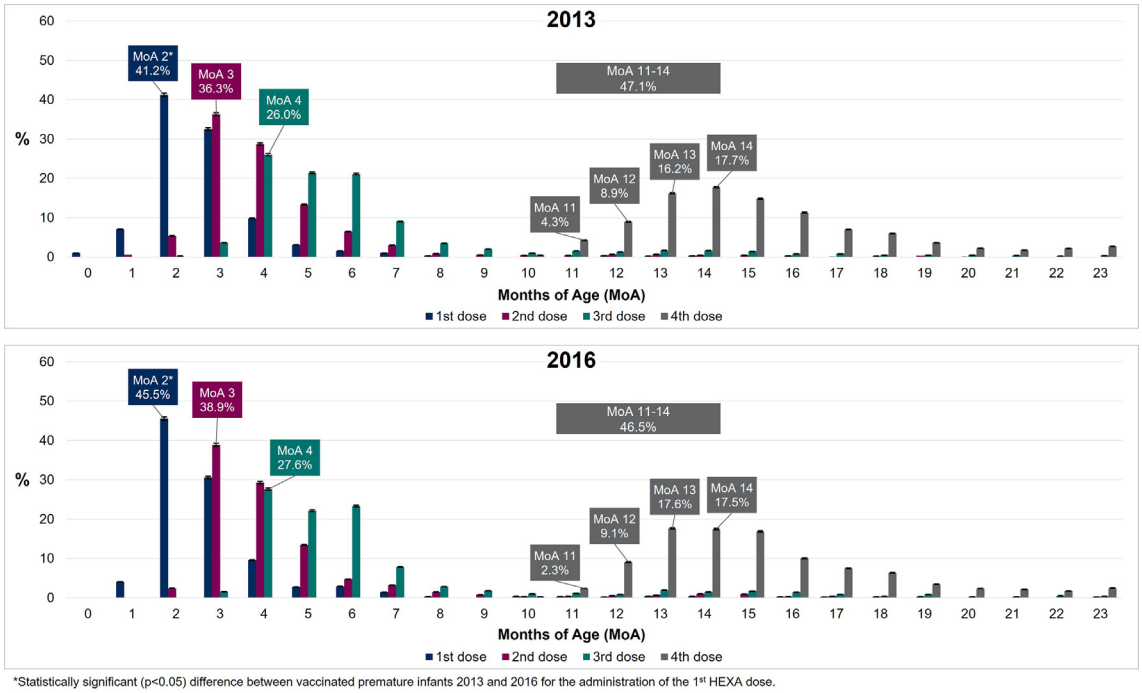


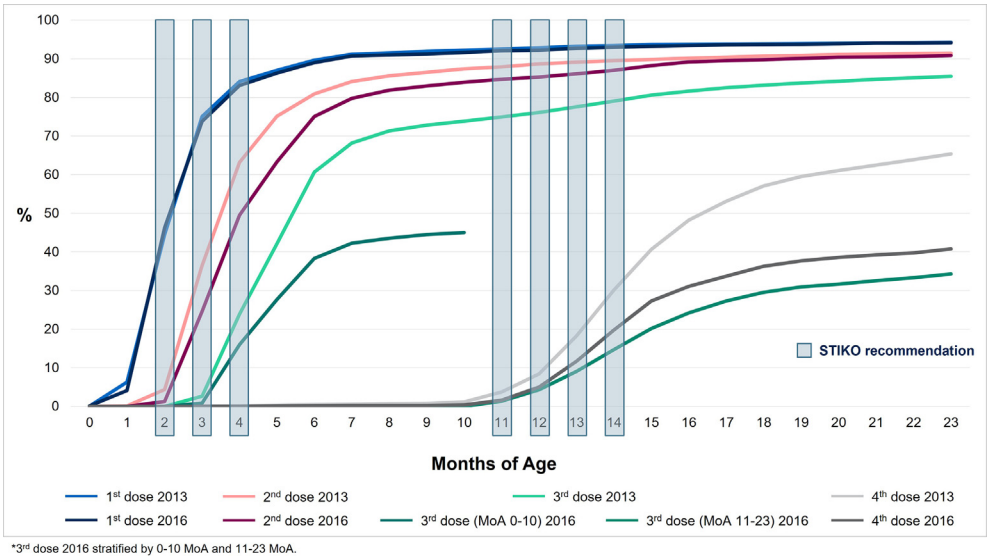
Fig. 3. Timeliness of HEXA vaccination until 23 months of age – premature infants 2013 and 2016.

time of administration in premature infants 2013 and 2016 (see Fig. 5).

4. Discussion

The present study determined vaccination rates for PCV and HEXA vaccination as well as the completeness and timeliness of the administered vaccines in premature infants in Germany. As claims data are collected primarily for reimbursement purposes, it was not possible to identify reasons why children did not receive an immunization or why vaccinations were delayed. When interpreting the results, further limitations due to the nature of the data must be considered as discussed in Laurenz et al. [11].

Within the InGef Research Database, approximately 7% and 5% of newborns of birth cohorts 2013 and 2016 were identified as premature infants. Own calculations based on different sources (e.g., hospital birth statistics, DESTATIS) revealed that 8–9% of infants were born prematurely in 2013 and 2016 in Germany [15–18].



*3rd dose 2016 stratified by 0-10 MoA and 11-23 MoA.

Fig. 4. Cumulative PCV rates of premature infants 2013 and 2016 until 23 months of age*.

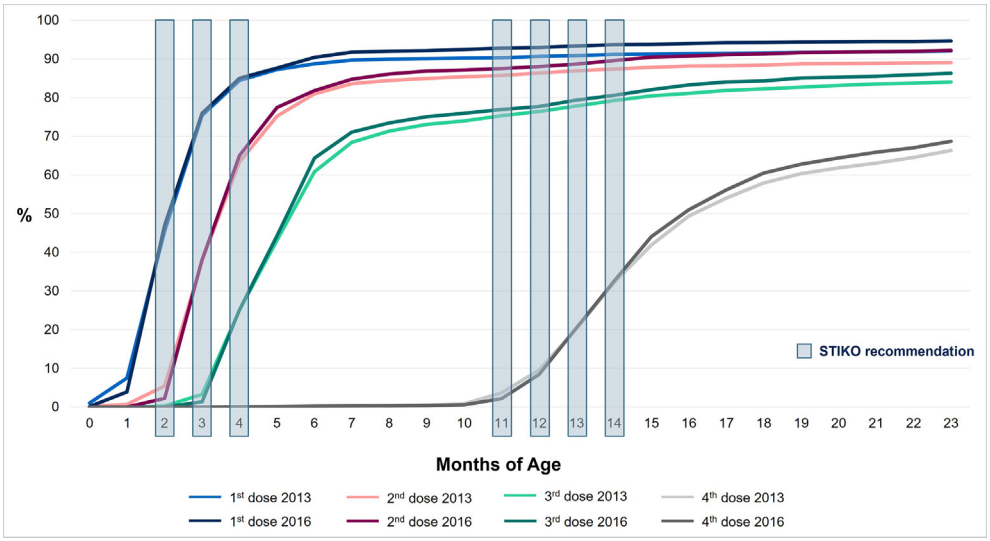


Fig. 5. Cumulative HEXA vaccination rates of premature infants 2013 and 2016 until 23 months of age.

As the identification of premature newborns in this study was designed in analogy to the definition of premature birth according to the World Health Organization (birth before 37 completed weeks of gestation) reflected in ICD-10-GM codes P07.2 and P07.3, ICD-10-GM diagnoses for an extreme low and low birth weight (P07.0 and P07.1) were not considered but coded in 5% of newborns in 2013 and 2016 according to DESTATIS [17,18]. Furthermore, the diagnoses codes of mothers, e.g., O09 on the duration of pregnancy, could not be used to validate the prematurity because a link between children and parents is not available in claims data. Other explanations for the difference include that while the InGef Research Database is representative in age- and gender for the general German population, it is not explicitly adjusted regarding newborns and therefore, the birth rate and thus the number of newborns in this research sample may differ. Furthermore, only premature infants who completed 24 months of follow-up were included in this study (exclusion of sickness fund switch and death). Additionally, the study only considered patients insured in one of the 60 SHIs covered in the database and it cannot be ruled out that the characteristics of the population groups covered might be slightly different from the general population. As the reasons for the lower number of premature infants might be multifactorial the extent of each factor could not be quantified here.

Until August 2015, the immunization of mature and premature infants against pneumococci was administered as 3+1 vaccination cycle. Since then, different vaccination schemes apply for the PCV of mature (2+1 scheme) and premature (3+1 scheme) infants in Germany. The STIKO's rationale for adjusting the PCV schedule included the assumption that a reduction of the recommended doses for mature infants would reduce the costs for PCV while potentially a higher acceptance for vaccination could be achieved. However, because the 2+1 scheme might be less effective compared with the 3+1 cycle, it could not be ruled out that additional IPD cases might occur within the 2+1 vaccination schedule [6].

The results of the present study could not confirm the assumption of increasing the share of PCV vaccinated children in both birth cohorts, since approximately 6% of premature newborns received no PCV. A slightly positive trend was visible

in unvaccinated newborns for HEXA vaccination (8% vs 5%). These results relate to those presented in Laurenz et al. [11], where vaccination rates in mature born infants were analyzed. Similarly, the share of mature newborns receiving no PCV remained constant (9%), while a slightly decreasing trend in unvaccinated infants (11% to 8%) was observable for HEXA vaccination. As no vaccination registry exists in Germany, only limited data on vaccination rates is available such as the vaccination surveillance of the Statutory Health Insurance (SHI) Physician Association or the results of the school entry examinations [19] where no distinction between premature and mature newborns is made. Consequently, these results are not comparable with the PCV and HEXA vaccination rates in premature infants obtained in this study.

This study indicated that about 65% of premature newborns in 2013 received the full PCV according to the STIKO recommendation, while this only applied to 41% of premature newborns in 2016. In light of the new recommended 2+1 PCV scheme in mature infants, a significant ($p < 0.05$) increase of mature children with full PCV immunization status was observed when comparing birth cohorts 2013 and 2016 (68% vs 76%) as shown in Laurenz et al. [11]. The findings highlight that more mature newborns in 2016 seem to be fully vaccinated compared to premature infants according to the respective recommendation. Contrarily, the full HEXA immunization rate in premature newborns with an unchanged 3 +1 recommendation for mature and premature infants experienced no significant changes over time (66% to 69%), while the full HEXA immunization in mature infants increased significantly (69% to 73%) [11].

The cumulative PCV rates in premature infants indicated that the 3rd and the 4th PCV dose in 2016 were administered later and less often in 2016 compared to 2013. About 34% of premature newborns in 2016 received their 3rd PCV dose at the age of ≥11 months and therefore, in the timeframe intended for the booster vaccination (11–14 MoA). Consequently, the recommended vaccination scheme for premature newborns has not been applied adequately and the 2+1 PCV schedule with administration of the booster vaccination at 11–14 MoA as intended for mature infants have been used.

Potential influence factors could include the physicians' medical assessment of premature infants, especially of infants with near-normal birthweight or born shortly before 37 weeks of gestation. Own calculations based on hospital birth statistics revealed that 83% of premature infants were born between the 32nd and 36th week of gestation in 2013 and 2016 [15,16]. Of high interest would be the discussion with pediatricians if there are reasons to follow the vaccination scheme for mature children depending on the perception of the child's development.

Premature infants are likely to stay longer in hospital after birth and the first vaccination cycle might be applied during the hospitalization [20]. As the identification of applied vaccines in the inpatient setting is not possible in claims data, we might underestimate the vaccination rates especially in extremely premature newborns and misclassify the actual 2nd PCV dose as the 1st dose. However, since PCV and HEXA vaccination doses are usually administrated concomitantly [21], the first HEXA vaccination might also have been applied already during the inpatient stay of birth resulting in the same misclassifications. Nonetheless, the comparison of premature children in 2013 and 2016 indicated no deviations from the 3+1 HEXA vaccination schedule so that the observable trend of PCV rates in premature infants might be rather associated with the STIKO recommendation modification for mature infants (reduction to 2+1 vaccination scheme).

Furthermore, our findings relate to studies from the United States, France, and Italy which indicate that many very preterm and low-birth weight infants are not sufficiently protected due to missing and delayed vaccination doses [22–24]. A reason for the observed delay or non-vaccination could be the fear of adverse events as an increase in cardiorespiratory events following immunization in extremely premature newborns is reported [25].

On the other hand, premature infants are known to have an increased risk of infectious diseases and show a significantly higher incidence rate of IPD [2,26]. An Australian study on hospital admissions due to infectious diseases in newborns revealed that the frequency of infection-related hospitalizations increased by 12% for each week reduction in gestational age before 39–40 weeks and by 19% for each 500 g reduction in birthweight <3,000–3,500 g [4]. Moreover, several studies reported that PCV was generally well tolerated in premature infants when administered on recommended schedule and that antibody responses were consistently higher after the booster dose was administered [3]. These findings support the importance of timely and complete PCV also in infants born prematurely.

5. Conclusion

Overall, premature infants received their PCV and HEXA vaccination doses later compared to mature born infants [11]. In a significant proportion, the PCV according to the 2+1 scheme recommended for mature infants has been applied in premature newborns. As concluded by Kent et al., the clinical relevance of these findings demands further research regarding a possible increased IPD incidence in premature infants since changes to the immunization schedule may disproportionally affect premature newborns [2]. Furthermore, a substantial share of premature children remained unvaccinated against pneumococci (about 6% in both cohorts) and against polio, diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b infections, and hepatitis B (8% in 2013 vs 5% in 2016). Further research is warranted to uncover the underlying reasons for the presented findings. Moreover, the STIKO changed the recommendation for the HEXA vaccination for mature infants from a 3+1 to a 2+1 schedule in June 2020 and maintained the 3+1 schedule for premature infants [27]. As our analysis of PCV indicated, future research should monitor whether the reduced HEXA vaccination schedule will be erroneously applied to premature infants as well. In conclusion, the findings advocate for further research to identify the reasons why the STIKO recommendations have not been adequately applied in premature infants and call for a stronger surveillance of vaccination rates, particularly to protect especially the most vulnerable populations such as premature born infants.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: M. Laurenz and C. von Eiff are employees of Pfizer Pharma GmbH. K. Schley is an employee of Pfizer Deutschland GmbH. K. Borchert, K. Seidel, and C. Jacob are employed by Xcenda GmbH which received consulting fees for the execution of the study and preparation of the manuscript from Pfizer Pharma GmbH, Germany.

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Dr. Julia Schiffner-Rohe contributed during the study initiation and development and reviewed the manuscript. The data analysis was performed in cooperation with Elsevier Health Analytics.

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Ethical approval

For this type of study formal consent is not required.

Data statement

A retrospective claims database analysis was conducted using anonymized claims from the "Institut für angewandte Gesundheitsforschung Berlin" (InGef) Research Database. The data used in this study cannot be made available in the manuscript, the supplemental files, or in a public repository due to German data protection laws (Bundesdatenschutzgesetz). To facilitate the replication of results, anonymized data used for this study are stored on a secure drive at the InGef. Access to the data used in this study can only be provided to external parties under the conditions of the cooperation contract of this research project and can be assessed upon request after written approval (info@ingef.de), if required.

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Modul 11

Burden of disease of reoperations in instrumental spinal surgeries in Germany

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ORIGINAL ARTICLE

Burden of disease of reoperations in instrumental spinal surgeries in Germany

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Abstract
Purpose To estimate the incidence of instrumental spinal surgeries (ISS) and consecutive reoperations and to calculate the related resource utilization and costs.
Methods ISS and subsequent reoperations were identified retrospectively using surgery codes in claims data. The study period included January 01, 2009 to December 31, 2011. The reoperation rate was calculated for 1 year after the primary ISS. Resource utilization and costs were analyzed by group comparison.
Results A total of 3316 incident ISS patients were identified in 2010 with an annual reoperation rate of 9.98 % (95 % CI 8.98–11.02 %). Mean costs per patient were €11,331 per ISS and €11,370 per reoperation, with €8432 directly attributed to the reoperation and €2938 to additional resources.
Conclusions Costs of ISS and subsequent reoperations have a significant impact on health insurances budgets. The annual cost of reoperations exceeds the direct cost of the primary surgery driven by the need for further inpatient and outpatient care.

Keywords Instrumental spinal surgeries · Reoperation · Resource utilization · Costs · Claims data

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Introduction

The aim of spinal fusion is to stabilize the spine by permanently combining at least two vertebrae. Several devices can be used to accomplish the instrumental fixation such as graft, supplementary bone tissue, rods, screws, plates or cages. Instrumental spinal surgery (ISS) may be indicated when sudden events such as injuries, fractures, or emerging events including infection, or tumors causing spinal weakness and instability occur. Furthermore, spine-related diseases such as spondylolisthesis, scoliosis, kyphosis, or spinal stenosis, are possible indications for ISS [1]. Due to the variety of indications, patients with the need for instrumental spinal surgeries are very heterogeneous and may vary from small children to frail elderly people [2–8].

The use of pedicle screws for the fixation of vertebrae in the thoracic and lumbar spine is a generally accepted ISS approach; however, the accurate placement of pedicle screws remains difficult in complex cases [9]. Misplaced screws might result in complications. In the case of transpedicular fixation, complication rates for deep tissue infection (4–5 %), cerebrospinal fluid leak (4 %), transient neuropraxia (2 %), and permanent nerve root injury (2 %), and instrumentation failure (3–12 %) have been reported [10]. Such scenarios impose a considerable burden on patients due to persistent pain and the potential need of further surgery [11, 12]. Reoperations might be necessary to correct pedicle screw malplacements and are associated with significant additional resource utilization and cost from the payer's perspective. Imaging techniques to assist the surgeon have the potential to reduce complications due to misplaced pedicle screws and may, therefore, have a positive impact on patients' well-being and payer budgets [13–17].

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ISS and consecutive reoperations have a considerable impact on healthcare budgets. A recent review by Alvin et al. presented international cost data for cervical and lumbar spine surgery. Hospital costs ranged from $9471 to $15,755 for cervical and from $4759 to $58,509 for lumbar spine surgery. From the payer perspective—depending on the follow-up period—costs for cervical spine surgery were between $4499 and $30,644 and differ from $18,159 to $31,175 for lumbar spine surgery with a maximum follow-up of 31 months. The societal costs for cervical spine surgery ranged from $10,783 to $15,714 and from $5476 to $90,036 for lumbar spine surgery, considering a follow-up of 12–60 months [18]. Over the last decade, the costs for spinal fusion surgery in the USA increased significantly to a total of $46.8 billion in 2010 [19, 20]. Average direct 2-year costs for revision lumbar fusion of $32,915 were reported by Parker et al. with a range from $24,935 to $63,769 [21]. Adogwa and colleagues calculated mean 2-year total cost of revision lumbar surgery of $28,256 for elderly patients [22].

Reliable data on incidence of ISS, the natural frequency of complications and the associated resource utilization and costs for reoperations are lacking for Germany. Also, the share of ISS performed with the guidance of imaging techniques in German hospitals has not been reported. The aim of this study was to estimate the incidence of ISS, the natural frequency of consecutive reoperation surgeries in patients with ISS, the associated resource utilization, explore the utilization of 3D-imaging and navigation systems at the time of the primary ISS, and to calculate the annual incremental cost of ISS reoperations.

Materials and methods

Data and study population

Anonymized claims data from the Health Risk Institute (HRI) research database were analyzed retrospectively in this observational study. The HRI database includes pooled claims data of around 80 different German health insurances covering 4.4 million lives. The participating health insurances operate nationwide. The data sample is representative for the German population in terms of age and gender [23].

The database contains information on all services reimbursed by the participating health insurances on an individual patient level. Furthermore, information on patients' demographics such as age and gender and acquired co-morbidities can be linked via a unique identification code.

The study period comprised the timeframe of January 1, 2009 to December 31, 2011 covering 4,431,636 individuals. We applied surgery and procedure codes (OPS, German adaptation of the International Classification of Procedures in Medicine, World Health Organization) to identify ISS and reoperations in the inpatient setting. ISSs were defined as one of the following OPS codes: 5-834 "Open reduction with internal fixation of the spine (osteosynthesis)", 5-835.0-9 "Osteosynthesis and bone substitutes at the spine", 5-836.3 "Spondylodesis (dorsal)", or 5-836.4 "Spondylodesis (dorsal and ventral combined, inter-corporal)". Patients were defined as incident patients if they had an ISS in 2010 (index date) and no ISS in the individual 12 months before the index date. The natural frequency of reoperations was calculated for an individual period of 12 months after the primary ISS in 2010 for each patient in the study population.

A broad approach was chosen to identify reoperations and the development of the algorithms to identify primary ISSs and following reoperations was guided by two clinical experts [Jörg Franke, Michael Winking]. Patients with an OPS code 5-839.5 "Revision of a spinal surgery" or 5-983 "Re-surgery" were considered to have had a reoperation. Moreover, patients with a sequence of the same access codes OPS codes 5-030* "patient access cervical spine", 5-031.0* "patient access thoracic" or 5-032.0* "patient access lumbar" at their primary surgery and at the consecutive secondary surgery were also included in this group.

Furthermore, the use of 3D-imaging, navigation systems, and intraoperative neurophysiological monitoring was investigated by checking for OPS 3-992 "Intraoperative use of 3D imaging", OPS 3-996 "Use of a 3D-Image converter", OPS 5-988 "Use of a navigation system", and OPS 8-925 "Intraoperative neurophysiological monitoring" at the time of the primary ISS.

Healthcare resource utilization and costs

Healthcare resource utilization (HRU) and costs were calculated from the perspective of the statutory health insurance (SHI); therefore, co-payments and out-of-pocket payments were not taken into account [24].

The measurement of healthcare resource use included the number of outpatient visits, inpatient visits, days in hospital, pharmaceutical prescriptions, therapeutic devices and remedies, days of incapacity to work, and days of paid sick leave. Reoperation specific resource utilization was calculated as the mean difference in each category between the non-reoperation group and the reoperation group.

All costs were calculated on an annual scale of 12 months before and 12 months after the primary ISS for each patient in the study population. Costs in Euro were extracted directly from the database. The costs of the primary ISS were attributed to the post index period in the

inpatient cost domain. Costs were calculated separately for each of the six domains—outpatient care, inpatient care, prescriptions, remedies, devices and aids and sick leave payments—and summed.

Cost of the primary ISS was calculated on the basis of reimbursed DRGs (Diagnosis Related Groups) for the corresponding hospitalization. Annual incremental cost of a reoperation was calculated by comparing patients with a reoperation to a control group comprising patients without a reoperation after their primary ISS. The mean cost difference between both groups was attributed to the reoperation. Usually, a matching algorithm is applied to control for existing differences in the characteristics of the individuals in the study group and those in the control group. These differences might bias the impact of an intervention. Matching the two groups, controls for that bias and the observed outcome can be attributed to the intervention [25]. In this study, the two groups were statistically comparable in terms of age and gender measured by the standardized difference to a 10 % level. No relevant differences in co-morbidities and pharmaceutical therapy were observed by the two clinical experts. Therefore, a matching of the two patient groups was not necessary.

The difference in differences approach was used to control for the impact of unobservable variables (e.g., patient behavior or physical constitution). Therefore, the difference in costs between the two groups in the year before the primary ISS was subtracted from the difference in costs between the two groups 12 months after the primary ISS. This was applied for each cost domain separately [26].

Results

A total of 3316 patients were identified having undergone ISS in 2010. The most common indications were "Deforming dorsopathies" (ICD-10: M40–M43) 22.3 %, "Spondylopathies" (ICD-10: M45–M49) 27.8 %, and "Other dorsopathies (ICD-10: M50–M54) 30.0 %. Fractures were reported less frequent with "Fracture of lumbar spine and pelvis" (ICD-10: S32) 7.7 % and "Fracture of rib(s), sternum and thoracic spine" (ICD-10: S22) 4.5 %. More than half of the study population was female (54.3 %), and the mean age was 61 years. Out of these, 331 patients underwent a reoperation within 12 months after their primary ISS resulting in an annual reoperation rate of 9.98 % (95 % CI 8.98–11.02 %). Patients with reoperations were comparable to those without a following reoperation in terms of age and gender. The standardized difference was 7 % for age and 4 % for gender. Reoperations were also more frequent for female patients (55.9 %) (Table 1).

Utilization of navigation and imaging techniques

In general, the use of navigation and imaging techniques was infrequently recorded for the study population at the time of the primary ISS (Table 2). The use of navigation and imaging techniques was slightly more frequent in the reoperation group with intraoperative 3D imaging, 3D-Image converter, and navigation system use. Intraoperative neurophysiological monitoring was more common in the non-reoperation group.

Annual resource utilization after primary surgery

On average, patients with ISS had frequent outpatient visits and numerous prescriptions of pharmaceuticals, remedies, and devices and aids (Table 3). Twenty seven percent (27 %) of the pharmaceutical therapy was pain medication including potent opioids.

Patients with reoperations used nearly twice (97.9 %) as many prescribed remedies and devices and aids as those without a reoperation. Prescriptions for pharmaceuticals were higher (34.6 %) in the reoperation group with 26 compared to 35 prescriptions (Fig. 1). As expected, patients undergoing a reoperation spent 23 days (104.5 %) more in the hospital than patients without a reoperation.

Cost of ISS and following reoperations

The mean cost per patient for an ISS was €11,331. Patients without a reoperation incurred €11,106, whereas patients with reoperations incurred a cost of €13,358. The difference was driven by 42.6 % of reoperations occurring within the same hospital stay as the primary ISS.

Combined with the costs of the primary ISS, patients with a reoperation had a mean total cost of €31,220 in the 12 months after their primary ISS. In contrast, the mean annual total cost of patients without a reoperation was €18,928; a difference of €12,291 ($p < 0.0001$) (Table 4).

We controlled for unobserved variables and identified a significant difference between the two groups in mean total costs in the year before ISS of €921 ($p = 0.0433$). Therefore, the difference in differences approach was applied to adjust the annual cost for reoperations. Table 5 shows the comparison of unadjusted and adjusted incremental costs in the 12 months after the primary ISS.

The adjusted total mean annual cost for a reoperation was €11,370. More than half of the reoperations (51.1 %) took place within a short period after the primary ISS. The majority of these cases (83.4 %) underwent the reoperation within the same hospital stay as the primary ISS was conducted; another 16.6 % of the patients were reoperated

Table 1 Study population demographics

Gender	Total ISS population		Patients not undergoing reoperation		Patients undergoing reoperation	
	N	%	*N*	%	*N*	%
Female	1803	54.37	1618	54.20	185	55.89
Male	1513	45.63	1367	45.80	146	44.11
Total	3316	100	2985	100	331	100
Age	Mean	SD	Mean	SD	Mean	SD
Female	61.67	15.30	62.94	16.08	61.53	15.20
Male	59.50	15.17	60.10	18.16	59.44	14.83
Total	60.68	15.28	61.69	17.06	60.57	15.07

ISS instrumental spinal surgery, *SD* standard deviation

Table 2 Utilization of navigation, 3D imaging and monitoring

Type of procedure	Non-reoperation group		Reoperation group	
	Cases	%	Cases	%
Intraoperative use of 3D imaging	44	1.47	12	3.63
Use of 3D imaging	17	0.57	3	0.91
Use of a navigation system	98	3.28	16	4.83
Intraoperative neurophysiological monitoring	57	1.91	4	1.21

Table 3 Resource utilization for ISS patients in 2010

	Mean (SD)	Min; max	Median
Outpatient care visits	15 (9)	0; 68	14
Prescribed packages	27 (25)	0; 223	21
WHO pain ladder step 1	4 (6)	0; 99	2
WHO pain ladder step 2	2 (4)	0; 63	0
WHO pain ladder step 3	1 (4)	0; 67	0
Number of remedies[a]	34 (109)	0; 2402	12
Number of devices and aids[b]	18 (170)	0; 3670	0
Days of incapacity to work	32 (71)	0; 366	0
Days of sick leave payment	27 (69)	0; 366	0
Hospitalization	2 (2)	0; 40	1
Days of hospitalization	25 (31)	0; 325	14

Max maximum, *Min* minimum, *SD* standard deviation, *WHO* World Health Organization

[a] Remedies (Heilmittel) are services like massages or occupational therapy provided by medically trained personal

[b] Devices and aids (Hilfsmittel) are devices such as walkers and wheel chairs to support the patient in recovery and every day care

within less than 30 days after discharge from hospital. In 48.9 % of all cases, the patient had already left hospital for more than 30 days when readmission and subsequent reoperation became necessary.

Due to the German DRG system, these three types of combined primary ISS with following reoperations are reimbursed differently by the Statutory Health Insurance. Cases where the reoperation took place within the same hospital stay (€17,056) or within less than 30 days after discharge from hospital (€17,857) receive lower reimbursement than cases where the primary ISS and the reoperation are more than 30 days apart (€21,988). The average reimbursement of an ISS with no following reoperation was €11,106 in the control group.

Discussion

Claims data are recorded for accounting purposes and not for clinical research. As a result, it is not possible to characterize patients by clinical parameters such as disease severity or to see the physician's intention for each intervention. It is, therefore, difficult to investigate plausible causes of reoperations based on claims data.

Nevertheless, the present study is the first scientifically published study for the German setting which analyses the incidence and costs of ISS and consecutive reoperations from the perspective of the SHI. Due to the nature of German claims data, the results provide a complete picture of the costs from the payer perspective. ISS and following reoperations have a considerable impact on health insurance budgets. The data sample in this study comprises nationwide operating health insurances and is representative for the Germen population in terms of age and gender.

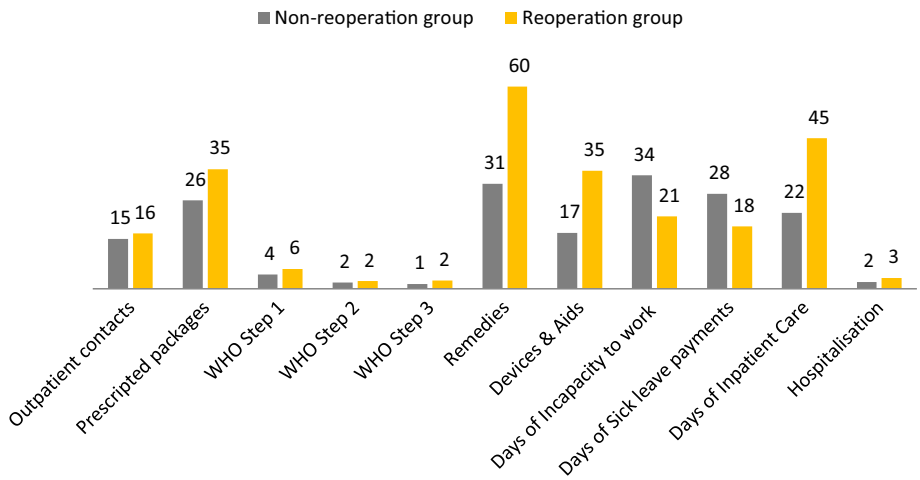

Fig. 1 Resource utilization comparison. Remedies (*Heilmittel*) are services like massages or occupational therapy provided by medically trained personal. Devices and aids (*Hilfsmittel*) are devices such as walkers and wheel chairs to support the patient in recovery and every day care. *WHO* World Health Organization

Table 4 Unadjusted mean cost comparison 12 months after the primary ISS

Cost domain	Non-reoperation group		Reoperation group		Incremental mean cost in €	*p* value
	Mean in €	Median in €	Mean in €	Median in €		
Outpatient care	988	756	1186	958	198	0.0034
Prescriptions	1127	454	1817	870	689	0.0027
Remedies	326	149	502	244	176	0.0001
Devices and aids	438	0	880	37	442	0.0058
Sick leave payments	1107	0	676	0	−431	0.0025
Inpatient care	14,941	10,020	26,159	19,860	11,218	<0.0001
Total	18,928	13,789	31,220	24,270	12,291	<0.0001

Table 5 Comparison of unadjusted and adjusted incremental costs

Cost domain	Unadjusted incremental mean cost in €	Adjusted incremental mean costs (DID) in €
Outpatient care	198	100
Prescriptions	689	240
Remedies	176	139
Devices and aids	442	378
Sick leave payments	−431	−354
Inpatient care	11,218	10,867
Total	12,291	11,370

DID difference in differences

With 10 % of all primary ISS patients requiring a reoperation, the aggregate annual costs for reoperations amounted to approx. €59.3 m from the perspective of the German SHI. Furthermore, the annual costs of the reoperation exceeded the cost of the primary ISS on the patient level. These costs are only partly attributable to the reoperation itself (€8432), but also to an increased need for further inpatient and outpatient care as well as a higher demand for medications, devices and aids, and remedies. Therefore, preventing reoperations might not only result in a reduction of direct costs of the surgery, but also reduce the need for other health services.

On average, total annual costs of patients undergoing ISS with and without following reoperations amounted to €20,155 in our study sample. In contrast, Ong et al. reported Medicare payments for older patients (65 years and older) with lumbar spinal fusion of $46,840 for a 1-year follow-up period [27]. Focusing on annual reoperation costs, the mean total costs of an ISS patients requiring reoperation resulted in €31,220 in this study whereas Parker et al. reported 2-year direct total costs of $32,915 for patients undergoing revision lumbar fusion [21]. A comparison of these costs is only possible to a limited extent due to the heterogeneity of the study populations and differences in the reimbursement scheme in Germany and the USA.

The natural frequency of reoperations in this study was estimated to be 9.98 %. A review of Watkins et al. 2010 reported reoperation rates from 10 to 42 % for studies using traditional techniques to insert pedicle screws and reoperation rates ranging from 0 to 9 % for studies where an imaging technique was used to guide screw application [17]. Possible clinical implications of the observed reoperation frequency might be complications such as

secondary infections, CSF leakages due to worsened clarity of the operation field, and prolonged nerve compression with the risk of a permanent neurological deficit due to an unsuccessful primary ISS.

The frequency of reoperations might vary due to numerous factors. US studies have reported different rates of reoperations for different parts of the country [28–30]. Surgical experience may also vary between different surgeons and hospitals. These aspects are not addressable in detail with claims data. However, regional differences are not a major concern in Germany and differences between hospitals and surgeons are negligible due to the nationwide data sample.

The broader approach of identifying reoperations was chosen here because of the hypothesis that current coding practice might be incomplete and not every reoperation is classified as such by the appropriate OPS code. The addition of the access codes identified further reoperations where no explicit reoperation code was recorded. Otherwise, not every case identified by the reoperation codes contains the access codes. This might affect the natural frequency of reoperations observed in this study.

More than half of the reoperations took place within a short time after the primary ISS; 42.6 % were carried out within the same hospitalization as the primary ISS, and 8.5 % within less than 30 days after hospital discharge. For reoperations within 30 days of hospital discharge after the primary ISS, a hospital receives a lower reimbursement rate from the health insurance than for a reoperation occurring after this 30-day period. These findings may have implications for hospital budgets and surgery volume.

The utilization of 3D-imaging, navigation systems, and intraoperative neurophysiological monitoring at the time of the primary ISS appears to be infrequent; however, it is unknown whether this is due to only occasional use of these techniques or incomplete coding/reporting practices. Coding might be incomplete if the hospital receives no incentive to record every OPS code related to the hospitalization, although there are strong coding regulations in place [31]. More frequent assistance with intraoperative navigation and imaging techniques in ISS might reduce the frequency of reoperations and the subsequent patient burden [1, 16, 32, 33].

Conclusion

The present study provides reliable information on the incidence of instrumental spinal surgeries and related reoperation for Germany. The direct costs of instrumental spinal surgeries have a significant impact on health insurances budgets. With 10 % of primary ISS patients requiring a reoperation, their associated annual costs are also relevant from the perspective of the statutory health insurance. On average, these costs exceed the direct cost for the initial surgery. Clearly, these costs are driven by the need for inpatient care. Nevertheless, costs for outpatient care also increase significantly in the year after the primary surgery. Further research is required to investigate the possible causes of reoperations. A better understanding of the underlying causes might help to improve ISS and avoid reoperations.

Conflict of interest Christian Jacob, Jennifer Scarlet Haas, and Sebastian Braun are employed by Xcenda GmbH. Xcenda GmbH received consulting fees for the conduct of the study from Medtronic International Trading Sàrl. Elena Annoni is an employee of Medtronic International Trading Sàrl. Michael Winking and Jörg Franke received consulting fees for supporting the study from Medtronic International Trading Sàrl.

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