Potenziale unterschiedlicher Datengrundlagen im Kontext von empirischen gesundheits- und versicherungsökonomischen Fragestellungen

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Zusammenfassung

Die sich wandelnden Rahmenbedingungen stellen Wissenschaftler und forschende Institutionen vor eine zunehmende Anzahl an Herausforderungen im Forschungsprozess. Diese Veränderungen werden unter anderem durch die Zunahme der Vielschichtigkeit der Datenquellen sowie Datenmenge, die steigenden regulatorischen Bedingungen sowie die wachsenden Anforderungen seitens der Projektträger getrieben. Als Konsequenz nimmt der Komplexitätsgrad innerhalb des Forschungsprozesses zu und impliziert einen höheren Planungsbedarf zu Projektbeginn.

In der vorliegenden Dissertation werden anhand selektiver Beispiele von quantitativen Forschungsvorhaben die konzeptionellen sowie methodischen Herausforderungen aufgezeigt und anschließend ausgewählte Limitationen dargestellt.

Insgesamt werden acht Publikationen für die Beantwortung der Forschungsfragen herangezogen, welche anhand der Art der Datenerhebung und Perspektive angeordnet sind. Die erste Arbeit basiert auf Primärdaten und adressiert eine Fragestellung der Gesellschaftsperspektive. Die beiden folgenden Publikationen inkludieren sowohl Primär- als auch Sekundärdaten und bearbeiten Fragestellungen aus der Perspektive der Patienten sowie Gesellschaft. In den weiteren fünf Veröffentlichungen werden Sekundärdaten als Grundlage verwendet. Zunächst wird eine Untersuchung anhand von Registerdaten aus der Patientenperspektive durchgeführt, bevor drei Analysen den Blickwinkel der Gesetzlichen Krankenversicherung mittels Routinedaten analysieren und abschließend eine gesellschaftliche Fragestellung unter Zuhilfenahme von Datenbanken sowie öffentlichen Statistiken beantwortet wird.

Die eingebrachten Module verdeutlichen einen Ausschnitt aus der Vielfalt an Möglichkeiten und Problemstellungen bei der Konzeption des Forschungsdesigns. Ausgehend von der Fragestellung wird zunächst betrachtet, welchen Einfluss diese auf die Auswahl der Datengrundlage hat. Darauf aufbauend wird dargestellt, wie diese beiden Aspekte die Methodik determinieren. Zuletzt erfolgt die Betrachtung der Limitationen, welche im jeweiligen Forschungsprozess aufgetreten sind und wie diese berücksichtigt wurden. Hierbei wurde die Verwendung von Mixed-Methods-Ansätzen als potentieller Lösungsansatz identifiziert.

Schlagwörter:
Gesundheitsökonomie, Versorgungsforschung, Sekundärdatenanalysen, Forschungsdesign

Abstract

The changing framework conditions confront researchers and corresponding institutions with an increasing number of challenges in the research process. These changes are driven, among other things, by the increase in the complexity of data sources and the amount of data, the rising regulatory conditions and the growing requirements on the part of project funding organisations. As a consequence, the degree of complexity within the research process is increasing and implies a higher need for planning at the beginning of the project.

In this dissertation, the conceptual and methodological challenges are illustrated using examples of quantitative research projects, followed by selected limitations.

A total of eight publications are included to answer the research questions, which are arranged according to the type of data collection and perspective. The first paper is based on primary data and addresses a question from the societal perspective. The two following publications include both primary and secondary data and address questions from the perspective of patients and society. In the other five publications, secondary data are used as the base. First, an investigation is carried out using register data from the patient's perspective, before three analyses examine the perspective of statutory health insurance using claims data, and finally a societal question is addressed with the help of databases and public statistics.

The modules presented here illustrate an excerpt from the variety of possibilities and problems in the conception of the research design. Starting with the research question, the influence of this question on the selection of the data basis is first considered. Building on this, it is shown how these two aspects determine the methodology. Finally, the limitations that arose in the respective research process and how they were taken into account are considered. In this context, the use of mixed-methods approaches was identified as a potential solution approach.

Keywords:
Health Economics, Health Services Research, Secondary Data Analyses, Research Design

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Abkürzungsverzeichnis

BaFin . . . . Bundesanstalt für Finanzdienstleistungsaufsicht

BeoNet . . . Beobachtungspraxen-Netzwerk-Register

bspw. . . . . beispielsweise

bzw. . . . . beziehungsweise

COPD . . . . chronisch obstruktive Lungenerkrankung

CT . . . . . Computertomographie

DCE . . . . . Discrete Choice Experiment

DSGVO . . . Datenschutz-Grundverordnung

EGFR . . . . Epidermal Growth Factor Receptor

FAIDS . . . Financial Almost Ideal Demand System

GKV . . . . Gesetzliche Krankenversicherung

HRQOL . . Health-related quality of life

ICD . . . . . International Statistical Classification of Diseases and Related Health Problems

IDC . . . . . International Data Corporation

KDD . . . . Knowledge Discovery in Databases

MRT . . . . Magnetresonanztomographie

OPS . . . . . Operationen- und Prozedurenschlüssel

ORR . . . . . Objective response rate

OS . . . . . Overall survival

PFS . . . . . Progression-free survival

PRISMA . . Preferred Reporting Items for Systematic reviews and Meta-Analyses

S. . . . . Seite

u.a. . . . . und andere

WHO . . . . World Health Organization

1 Motivation und Zielsetzung

Die sich wandelnden Rahmenbedingungen stellen Wissenschaftler und forschende Institutionen vor eine zunehmende Anzahl an Herausforderungen im Forschungsprozess: Die stetige Zunahme an Daten, steigende regulatorische Bedingungen sowie wachsende Anforderungen der Stakeholder können hierbei stellvertretend angeführt werden. Hinsichtlich der Daten bestehen dabei vielfältige, zum Teil sich gegenseitig bedingende respektive verstärkende, Aspekte. Die verfügbaren Datenmengen nehmen stetig zu,[1] wobei gleichzeitig auch die Menge der potenziellen Datenquellen und, damit einhergehend, Datenhalter ansteigt. Insbesondere das Internet of Things kann an dieser Stelle genannt werden, bspw. Wearables im Bereich des Gesundheitswesens und Telematik/Smart Home im Bereich des Versicherungswesens. Als Konsequenz daraus nimmt der Grad an unstrukturierten bzw. nicht-standardisierten Daten zu. In regulatorischer Hinsicht sind die zunehmenden Datenschutzbedingungen zu nennen, insbesondere im europäischen Raum die DSGVO[2]. In Bezug auf die Stakeholder können wiederum mannigfaltige Dimensionen betrachtet werden: Zum einen besteht heutzutage in vielen Forschungsgebieten eine breite Evidenz im Bereich der Grundlagenforschung und zum anderen können aufgrund des technologischen und methodischen Fortschritts spezifischere Forschungsfragen untersucht werden. Als Folge dessen steigen die Anforderungen, was sich bspw. in den Vorgaben und Ausschreibungen von öffentlichen Projektträgern wiederspiegelt. Die vorgenannten Aspekte implizieren, dass die Komplexität innerhalb des Forschungsprozesses steigt und der Planung zu Projektbeginn eine höhere Bedeutung beigemessen werden sollte.

Die Konzeption des Forschungsdesigns stellt das verbindende Element zwischen dem identifizierten Forschungsproblem sowie der Durchführung der Untersuchung dar und soll sicherstellen, dass die gewonnenen Erkenntnisse zum einen die Fragestellung adäquat adressieren und zum anderen valide sind. Die Research Onion nach Saunders[3] stellt ein globales Konstrukt für die Vorgehensweise bzw. zu beachtenden Aspekte bei der Erstellung eines Forschungsdesigns

1 Das Weißbuch der IDC prognostiziert einen Anstieg der globalen Datensphäre von 33 Zettabyte im Jahr 2018 auf 175 Zettabyte im Jahr 2025, wobei von einer Steigerung von 36 Prozent im Bereich des Gesundheitswesens ausgegangen wird. Vgl. hierzu Reinsel u. a. 2018, S. 3, 6, 22.

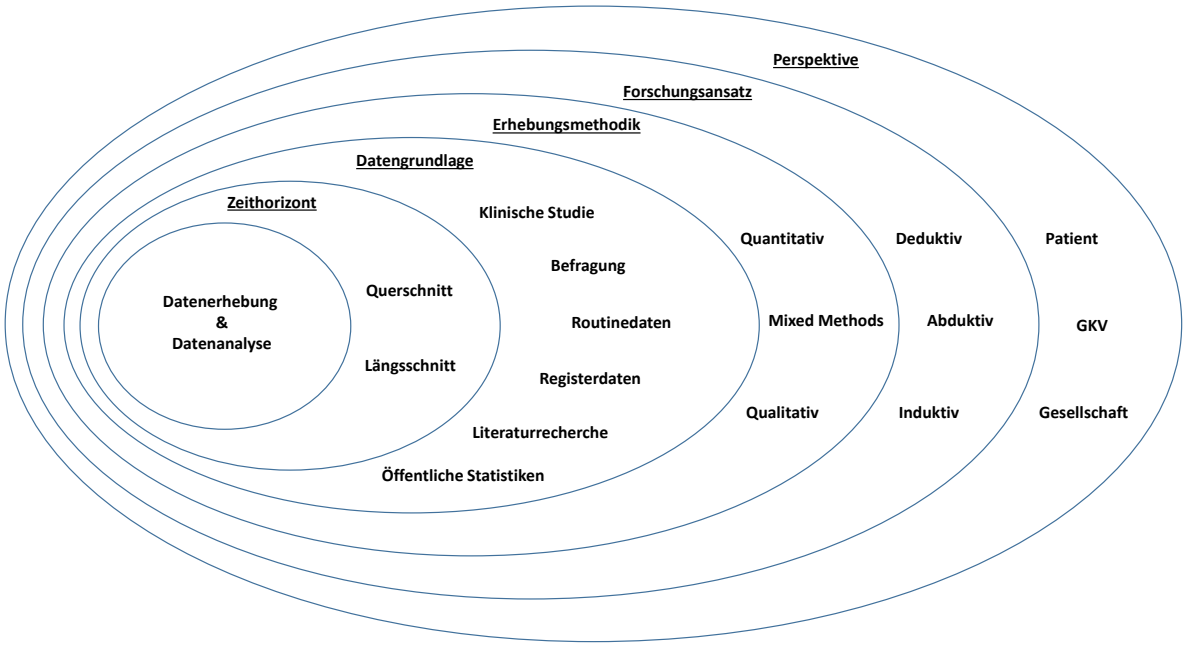
2 Exemplarische Beispiele für daraus resultierende Herausforderungen aus dem Bereich der medizinischen Forschung werden in dem Zeitungsartikel von Heller 2021 dargestellt.

3 Vgl. hierzu Saunders u. a. 2019.

dar. Im folgenden wird dieses, in einer für die Inhalte dieser Dissertation modifizierten Form, kurz vorgestellt und darauf basierend die Forschungsfragen abgeleitet. Abbildung 1 illustriert die unterschiedlichen Phasen und die dazugehörigen Ausprägungen, wobei diese aufeinander aufbauen und von außen nach innen definiert werden müssen.

Ausgehend von dem definierten Forschungsproblem erfolgt zunächst die Wahl der Perspektive[4] wobei im Kontext dieser Dissertation insbesondere die Ebenen des Patienten, der GKV bzw. des Kostenträgers sowie der Gesellschaft relevant sind. Auch wenn dies im ersten Moment trivial erscheint, ist eine klare Definition für die weiteren Phasen notwendig, da bspw. Kostenanalysen aus Gesellschaftsperspektive die indirekten Kosten beinhalten, wohingegen diese aus der Sicht der GKV nicht relevant sind.

Abbildung 1: Adaption der Research Onion



Quelle: Eigene Darstellung in Anlehnung an Saunders u. a. 2019, S. 130.

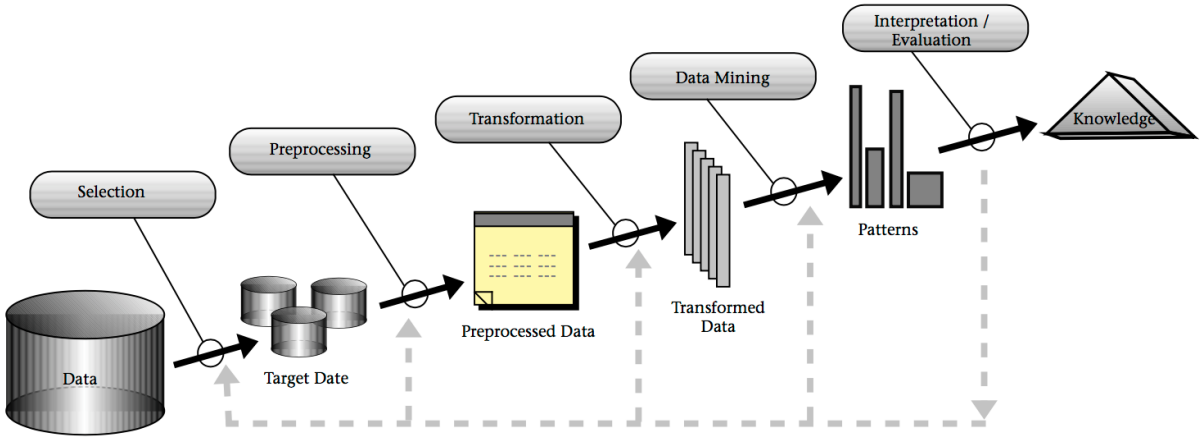
Der Forschungsansatz definiert die übergeordnete Zielstellung des Prozesses. Hierbei wird unterschieden in die Prüfung einer bestehenden Theorie respektive Hypothesen (Deduktion), die Entwicklung einer Theorie (Induktion) oder dem Generieren einer erklärenden Hypothese (Abduktion). Bei der Wahl der Erhebungsmethodik wird basierend auf dem Forschungsziel ebenfalls eine dreistufige Unterteilung vorgenommen. Entweder werden die Daten dabei standardisiert, systematisch und numerisch erfasst (Quantitativ) oder nicht-standardisiert (Qualitativ) oder beide Verfahren werden miteinander kombiniert (Mixed Methods). Hinsichtlich der Datengrundlage[5]

4 In der originären Version erfolgt in dieser Schicht die Definition der Philosophie der Herangehensweise.
5 In der originären Version erfolgt in dieser Schicht die Auswahl der Forschungsstrategie.

kann zunächst eine Unterscheidung in die Oberkategorien der Primär- bzw. Sekundärdaten vorgenommen werden. Hierbei sind Primärdaten dadurch gekennzeichnet, dass sie erstmalig und spezifisch im Rahmen der Studie/des Projektes erhoben werden, wie bspw. bei Befragungen und klinischen Studien. Im Gegensatz dazu werden Daten, die zu einem anderen Zweck erhoben wurden als Sekundärdaten bezeichnet, wobei zusätzlich noch Differenzierungen anhand des Grades der Aufbereitung sowie Aggregation bzw. damit erfolgter Analysen vorgenommen werden können. Register- respektive Routinedaten stellen hierbei Beispiele für einen geringen Aggregationsgrad dar, wohingegen öffentliche (amtliche) Statistiken oder Literaturrecherchen eher einem hohen Aggregationsgrad unterliegen. Die Wahl des Zeithorizontes ist die letzte Schicht vor der Datenerhebung sowie Datenanalyse und gliedert sich in mehrfache (Längsschnitt) bzw. einmalige Erhebungen (Querschnitt).

Während die Ausprägungen innerhalb der äußeren drei Schichten in weiten Teilen frei miteinander kombinierbar sind, definieren die dort gewählten Ausgestaltungen die Optionen innerhalb der nachfolgenden beiden Schichten. Das Zusammenspiel der fünf um den Kern liegenden Schichten bildet die Konzeption des Forschungsdesigns, welches dann im Schritt der Datenerhebung und Datenanalyse operationalisiert wird. Diese Schicht beinhaltet selbst einen komplexen Aufbau mit unterschiedlichen Phasen, welcher beispielhaft im KDD-Prozess nach Fayyad (siehe Abbildung 2) systematisch dargestellt wird.[6] Ausgehend von den erhobenen Daten (Data)

Abbildung 2: KDD-Prozess



Quelle: Fayyad u. a. 1996, S. 41.

erfolgt zunächst die Datenaufbereitung (Selection, Preprocessing und Transformation), bevor die spezifische Datenanalyse (Data Mining) durchgeführt wird und darauffolgend die Bewertung (Interpretation/Evaluation) der Ergebnisse. Die iterative Struktur des Prozesses ist hierbei ein wesentliches Element und stellt sicher, dass nach jeder Phase ein Abgleich hinsichtlich der Zielvorgabe erfolgt und, sofern notwendig, ein oder mehrere Prozessschritte erneut und

6 Der KDD geht hierbei von Sekundärdaten, insbesondere Datenbanken, aus. Für Primärdaten muss dieses Schemata entsprechend modifiziert oder ein anderes angewendet werden.

modifiziert durchgeführt werden. Im Schritt der Datenanalyse kann dabei das vollständige Methodenspektrum[7] eingesetzt werden, wobei die Auswahl in Abhängigkeit der vorliegenden Datenstrukturen sowie Zielstellung erfolgt.

In den vorhergehenden Abschnitten wurden die Prozesschritte zur Konzeption eines Forschungsdesigns sowie dessen Umsetzung anhand des Konstruktes der Research Onion sowie des KDD kurz exemplarisch veranschaulicht, wobei dies jeweils den idealtypischen Ablauf beschreibt. In der realen Umsetzung von Forschungsprojekten ergeben sich jedoch zahlreiche Herausforderungen hinsichtlich des idealtypischen Ablaufes, welche zumeist die Datengrundlage und/oder Änderungen der Rahmenbedingungen betreffen und daher als limitierende Faktoren wirken.

Die Dissertation verfolgt deshalb die folgenden Forschungsfragen:

1. Wie beeinflusst das Spektrum der Fragestellungen die Auswahl der Datenquellen und die damit einhergehenden Strukturen?

2. Welche methodischen Aspekte ergeben sich aus der Fragestellung und Auswahl der Datengrundlage?

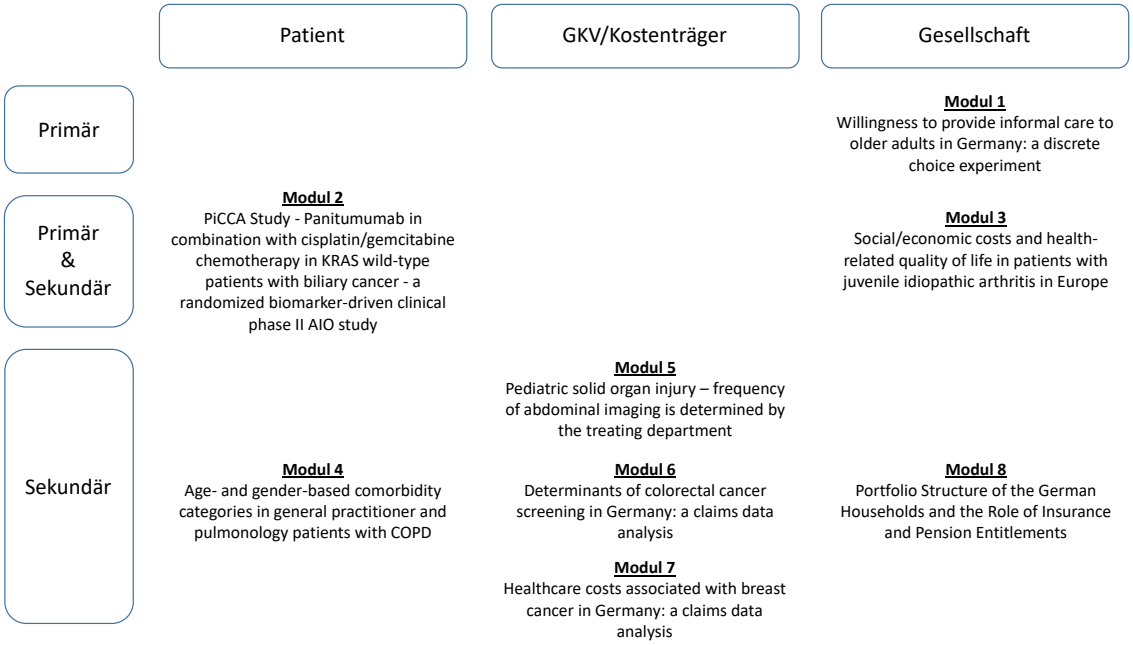
3. Welche Limitationen resultieren aus den verwendeten Datengrundlagen und wie können diese adressiert werden?

7 An dieser Stelle sei beispielhaft auf das Review von Mihaylova u. a. 2010 verwiesen, welches für den Bereich der Gesundheitsökonomie einen umfassenden Überblick der Methoden sowie den Voraussetzungen und damit verbundenen Vor-/Nachteilen bietet.

2 Beitrag der vorliegenden kumulativen Dissertation

Die vorliegende Dissertation gliedert sich in acht Module (siehe Abbildung 3), welche sich anhand ihrer Zuordnung zur Perspektive der jeweiligen Fragestellung sowie des verwendeten Ansatzes der Datenerhebung schematisch darstellen lassen. Hierbei erfolgt die Anordnung zunächst innerhalb der Dimension der Datengrundlage von Primärdaten zu Sekundärdaten und innerhalb dieser von der Mikro- zur Makroebene.

Abbildung 3: Module der Dissertation



Quelle: Eigene Darstellung.

Im Folgenden werden die Module und ihr jeweiliger Beitrag zur Dissertation kurz einzeln beschrieben. Die Charakterisierung folgt hierbei einem konsistenten Schema, indem zunächst das Ziel, dann die Datengrundlage sowie Methodik und abschließend die zentralen Ergebnisse präsentiert werden.

Mit der Veröffentlichung „Willingness to provide informal care to older adults in Germany - a discrete choice experiment“ (Modul 1) wurde untersucht, welche Attribute die Bereitschaft zur informellen Pflege determinieren. Aufgrund des mit der demografischen Entwicklung einhergehenden steigenden Pflegebedarfes und der Präferenz der Pflegebedürftigen in ihrem gewohnten Umfeld altern zu können, welche zudem mit dem Vorsatz „ambulant vor stationär“ politisch gewollt ist, nimmt insbesondere die Nachfrage nach informeller Pflege zu. Da jedoch schon ein Nachfrageüberschuss existiert, ist es aus gesellschaftlicher Perspektive notwendig, die Faktoren für die Bereitschaft zu eruieren, um Handlungsempfehlungen ableiten zu können.
Für die Erhebung der Präferenzen wurde, in Kooperation mit der AOK Niedersachsen, eine geschichtete Zufallsstichprobe der Allgemeinbevölkerung postalisch einmalig befragt. Die Analyse erfolgte auf Basis eines DCE mittels bedingter logistischer Regression und latenter Klassenanalyse. Für die Entwicklung des DCE wurden zunächst eine systematische Literaturrecherche und semi-strukturierte Interviews durchgeführt, um die relevanten Attribute, insbesondere mit Bezug zur informellen Pflege, zu identifizieren. Durch die Integration des Attributes „monetäre Entschädigung“ kann für die Einflussfaktoren und deren Ausprägungen die jeweilig notwendige Lohnersatzleistung bzw. die vorhandene marginale Zahlungsbereitschaft identifiziert werden.
Die Ergebnisse der bedingten logistischen Regression zeigen, bezogen auf das jeweilige Referenzniveau, dass der Faktor Entlastung, sowohl durch professionelle Unterstützung als auch Urlaubszeiten, einen positiven Einfluss und der zeitliche Aspekt, dargestellt durch den täglichen Umfang und den Zeitraum, einen negativen Einfluss auf die Bereitschaft zur informellen Pflege haben. Damit einhergehend reflektieren die Entlastungsleistungen eine Zahlungsbereitschaft zwischen 4,5 und 10,7 € je Stunde und die zeitlichen Faktoren die Erwartung einer finanziellen Kompensation zwischen 3,4 und 14,5 €, welche somit zum Teil oberhalb des gesetzlichen Mindestlohns liegt. Die Resultate der latenten Klassenanalyse zeigen jedoch die Heterogenität bezüglich der Präferenzen sowie insbesondere der Anreizwirkung der Lohnersatzleistung auf und verdeutlichen, dass die Verallgemeinerung der Ergebnisse auf die Gesamtstichprobe nicht möglich ist.

Im Gegensatz zu Modul 1, welches auf Primärdaten basiert, werden in den Modulen 2 und 3 Publikationen dargestellt, die sowohl Primär- als auch Sekundärdaten als Grundlage verwenden.

Das Ziel der Studie „PiCCA Study - Panitumumab in combination with cisplatin/gemcitabine chemotherapy in KRAS wild-type patients with biliary cancer - a randomized biomarker-driven clinical phase II AIO study “ (Modul 2) bestand in der Analyse der Effektivität einer erweiterten kombinierten Chemotherapie. Hierbei wurde die Wirkung des monoklonalen EGFR-Antikörpers Panitumumab als Ergänzung der standardmäßigen kombinierten Chemotherapie mit Gemcitabine und Cisplatin beim Gallengangkrebs bei Patienten mit Wildtyp-KRAS untersucht. Durch die zusätzliche Gabe des Antikörpers soll der EGFR Signalweg blockiert werden, welcher einen negativen Einfluss auf das Wachstum von Tumorzellen und somit auch die Bildung von Metastasen

haben kann.
In dieser offenen klinischen Phase II Studie wurden Patienten im Verhältnis von 2 zu 1 auf einen Behandlungsarm mit bzw. ohne Panitumumab randomisiert, wobei zur Berücksichtigung der Konstitution des Patienten eine Stratifizierung anhand des Niveaus von Leukozyten und alkalischer Phosphatase erfolgte. Zur Messung der Effektivität wurde als primärer Endpunkt das PFS nach 6 Monaten herangezogen und zudem als sekundäre Endpunkte die ORR, das mediane PFS, das OS sowie die Erfassung der Toxizität. Die Patientencharakteristika und Toxizität wurden mittels nicht-parametrischer Methoden und die Ereigniszeitanalysen mit der Kaplan-Meier-Methode untersucht. Um die Studienergebnisse in die bestehende Evidenzlage einordnen zu können, wurde zudem eine Metaanalyse, gemäß dem PRISMA-Schema, zu Studien von Chemotherapien mit und ohne EGFR-Antikörpern inkludiert. Hierbei wurden zunächst die bedingten Überlebenswahrscheinlichkeiten aus den Studien rekonstruiert, dann unter Berücksichtigung der divergierenden Beobachtungszeiträume gepoolt, darauf basierend die zusammengeführten Überlebenskurven erstellt und abschließend unter Verwendung von Bootstrapverfahren die Robustheit überprüft.
Im Studienverlauf wurden 90 Patienten eingeschlossen, welche im Median 7 Behandlungszyklen erhielten mit einer medianen Behandlungsdauer von 4,7 Monaten. Die PFS-Rate nach 6 Monaten betrug 54% bei der Behandlung mit dem EGFR-Antikörper gegenüber 73% ohne diesen und auch bei den weiteren Endpunkten zeigte sich keine Verbesserung durch die Gabe von Panitumumab. In Übereinstimmung mit den hier gezeigten Ergebnissen zeigt die Metaanalyse, basierend auf 12 identifizierten Studien, keinen Überlebensvorteil für die Patienten.

Im Rahmen eines europäischen Projektes entstand die Publikation „Social/economic costs and health-related quality of life in patients with juvenile idiopathic arthritis in Europe“ (Modul 3), in welcher die wirtschaftlichen Belastungen durch Patienten mit juveniler idiopathischer Arthritis aus gesellschaftlicher Perspektive sowie deren gesundheitsbezogene Lebensqualität ermittelt wurden. Neben der systematischen Erfassung der Ressourcenverbräuche stand hierbei die Identifikation von potentiellen Kostentreibern im Fokus der Analysen. Durch die zusätzliche Erhebung der HRQOL sollten zudem mögliche Korrelationen mit dem jeweiligen Behandlungsregime untersucht werden.
Als Grundlage für die länderspezifischen Analysen dienten Fragebögen, in denen von den Patienten und/oder ihren Betreuern retrospektiv die Daten zu demografischen Merkmalen, Inanspruchnahmen, informeller Pflege und Produktivitätsverlusten sowie HRQOL erhoben wurden. Basierend auf Literaturrecherchen und Datenbanken wurden länderspezifische Einheitskostensätze für die direkten und indirekten Kosten generiert und für die Bewertung der Ressourcenverbräuche angewandt. Der EQ-5D-5L wurde als generisches Instrument zur Ermittlung der HRQOL eingesetzt, der Barthel-Index für die Bewertung der Pflegebedürftigkeit und das Zarit Burden Interview zur Erfassung der subjektiven Belastung informell pflegender Angehöriger. Die Auswertung der Querschnittsstudie erfolgte deskriptiv.

In die Studie konnten 162 Patienten aus 6 Ländern eingeschlossen werden und die Resultate zeigen erhebliche Unterschiede zwischen den Ländern auf. Dabei variieren sowohl die direkten jährlichen (Nicht-) Gesundheitskosten als auch die indirekten Kosten. Der Vergleich mit früheren Studienergebnissen zeigt, dass die gesellschaftlichen Kosten im Zeitverlauf angestiegen sind. Hierfür konnten die Inklusion der Kosten informeller Pflege, die Zunahme der Krankenhausaufenthaltsdauer und die erhöhte Inanspruchnahme von Biologika als Kostentreiber identifiziert werden. Die Ergebnisse in Bezug auf die HRQOL zeigen eine Verschlechterung auf, wobei ebenfalls länderspezifische Divergenzen identifiziert wurden, welche in Teilen durch eine variierende Altersstruktur zwischen den Studienpopulationen erklärt werden kann.

Im Kontrast zu den drei zuvor dargestellten Modulen folgen nun die Publikationen, welche ausschließlich auf Sekundärdaten basieren. Hierbei inkludieren die Auswertungen in den Modulen 4 und 5 jeweils einen spezifischen Leistungssektor.

Die Publikation „Age- and gender-based comorbidity categories in general practitioner and pulmonology patients with COPD“ (Modul 4) adressiert die Fragestellung der Struktur der Komorbiditätslast bei COPD. Diese progressive Erkrankung stellt gemäß der WHO eine der häufigsten Todesursachen dar und gilt gemeinhin als Volkskrankheit. Es besteht Evidenz dahingehend, dass Tabakkonsum als eine der Hauptursachen gilt, die Prävalenz mit zunehmendem Alter ansteigt und COPD Patienten aufgrund des Mechanismus der systemischen Entzündung oftmals unter weiteren chronischen Erkrankungen leiden, wodurch das Behandlungsmanagement erschwert wird. Hinsichtlich der Komorbiditäten erfassen bisherige Studien jedoch nur einzelne Aspekte zur Stratifizierung oder sind auf wenige chronische Erkrankungen begrenzt. Das Ziel der Analyse bestand daher in der systematischen Erfassung der Komorbiditäten stratifiziert nach Alter, Geschlecht und Arzttyp (Allgemeinmedizin versus Pneumologie), wodurch das Behandlungsmanagement verbessert und dadurch die Lebensqualität der Patienten erhöht werden soll.
Die Auswertung basiert auf der Datenbank des BeoNet-Register. Dieses umfasst retrospektiv und routinemäßig erfasste Daten der elektronischen Patientenakten von kooperierenden niedergelassenen Hausärzten, Pneumologen und Pädiatern in pseudonymisierter Form. Für die Analysen der Längsschnittdaten wurde zunächst ein Algorithmus zur Identifikation von COPD Patienten entwickelt, Altersgruppen definiert und die Operationalisierung der Komorbiditäten erfolgte anhand der ICD Kodierung, wobei zwei Instrumente zur Anwendung kamen: die Klassifikation von 60 chronischen Erkrankungen nach Calderon-Larranaga[8] und der Elixhauser-Index[9]. Die generierten Daten wurden zum einen deskriptiv und zum anderen mittels Hypothesentests bzw. Varianzanalyse untersucht.
Aus den Ergebnissen konnten insbesondere drei zentrale Feststellungen abgeleitet werden: Die An-

8 Vgl. hierzu Calderón-Larrañaga u. a. 2017.
9 Vgl. hierzu Elixhauser u. a. 1998.

zahl der Komorbiditäten unterscheidet sich nicht zwischen den Geschlechtern, jedoch die Art und damit einhergehend auch die Bewertung mittels des Elixhauser-Index. Erwartungsgemäß steigt die Anzahl mit zunehmendem Alter, allerdings weisen auch schon die jüngeren Altersgruppen eine erhebliche Anzahl an Komorbiditäten auf. Zwischen den Arzttypen liegt ein abweichendes Dokumentationsverhalten hinsichtlich der Art und Anzahl an Komorbiditäten vor, welches beim Versorgungsmanagement und der Bewertung von Studienergebnissen berücksichtigt werden sollte.

Im Mittelpunkt der Veröffentlichung „Pediatric solid organ injury - frequency of abdominal imaging is determined by the treating department“ (Modul 5) stand der Vergleich des Einsatzes von CT bei Kindern mit Verdacht auf abdominale Traumata in Abhängigkeit der behandelnden Abteilung im stationären Sektor. Abdominale CT stellen aufgrund ihrer hohen Detektionsrate aktuell den Goldstandard dar und haben sich im Zeitverlauf in der Anwendung etabliert. Da Kinder jedoch potentiell anfälliger für Langzeitfolgen durch Strahlenbelastung, insbesondere bösartige Neubildungen, sind, sollte die CT-Bildgebung wenn möglich durch MRT substituiert werden. Die Intention der hier vorliegenden Untersuchung besteht daher in der Identifikation von möglichen Unterschieden beim Einsatz des abdominalen CT zwischen nicht-pädiatrischen und pädiatrischen Abteilungen.
Für die Analysen wurden Routinedaten des stationären Sektors der AOK Niedersachen sowie AOK Plus verwendet. Dabei erfolgte die Identifikation der Patienten basierend auf der ICD-10 Kodierung und der bildgebenden Verfahren, CT respektive MRT, auf der OPS Kodierung. Für die deskriptiven Auswertungen wurden Hypothesentests herangezogen und der mögliche Einfluss von soziodemografischen Faktoren sowie klinischen Daten mittels logistischer Regression analysiert. Die deskriptiven Ergebnisse zeigen, basierend auf 524 Patienten, dass die CT-Rate zwischen den nicht-pädiatrischen und pädiatrischen Abteilungen deutlich variiert. Die logistische Regression schätzt ein OR von 6,15 für den Einsatz des CT in der Allgemein-/Unfallchirurgie gegenüber der Kinderchirurgie unter Berücksichtigung der weiteren unabhängigen Variablen. Die Resultate deuten daraufhin, dass die konsistente Anwendung von evidenzbasierten Leitlinien zur Reduktion des Einsatzes des CT führen kann, wobei dieser Effekt durch die Zentralisierung der Verdachtsfälle unterstützt werden könnte.

Die Module 6 - 8 integrieren mehrere Leistungssektoren (Modul 6 und 7) respektive unterschiedliche Quellen (Modul 8).

Im Rahmen der Publikation „Determinants of colorectal cancer screening in Germany: a claims data analysis“ (Modul 6) war es das Ziel, die Einflussfaktoren auf die Inanspruchnahme von Präventionsleistungen zur Früherkennung des kolorektalen Karzinoms, dem fäkalen Okkultbluttest und der präventiven Koloskopie, zu ermitteln. Trotz Evidenz hinsichtlich ihrer Effektivität und einem positiven Kosten-Nutzen-Verhältnis zeigen die empirischen Inanspruchnahmeraten jedoch,

dass die präventive Koloskopie auf einem niedrigen Niveau verharrt und der fäkale Okkultbluttest im Zeitverlauf abnimmt. Aus der Perspektive der GKV resultiert somit ein Interesse an der Identifikation potentieller Einflussfaktoren, um die Inanspruchnahmeraten zu steigern und damit einhergehend die Allokation der Ressourcen zu optimieren. Aufgrund der schon bestehenden Evidenzlage liegt ein besonderer Fokus dieser Publikation auf der Berücksichtigung der Variablen zum Bildungsstatus und der Staatsangehörigkeit.
Die Ausgangsbasis für die Analysen bilden sektorenübergreifende Routinedaten der AOK Niedersachsen für den Zeitraum 2014 - 2016. Die Selektion der Versicherten für die Untersuchungskollektive basiert auf komplexen Ein- und Ausschlussalgorithmen, welche unterschiedliche Ziele verfolgen: Reduktion auf die anspruchsberechtigten Versicherten, Ausschluss von Versicherten mit darmspezifischen Vorerkrankungen bzw. mit diagnostischen Leistungen und Zuordnung der Versicherten in ein Studienkollektiv für den Okkultbluttest bzw. die Koloskopie. Die Untersuchung des Einflusses von soziodemografischen Faktoren auf die Inanspruchnahme erfolgt mittels multivariater logistischer Regressionen.
Die Studienergebnisse illustrieren signifikant abweichende Entwicklungen hinsichtlich der Präventionsleistung in Abhängigkeit unterschiedlicher Kovariaten. Bei der Koloskopie sinken die Chancen für die Teilnahme mit steigendem Alter bei beiden Geschlechtern, wohingegen beim fäkalen Okkultbluttest mit steigendem Alter die Chance bei Männern steigt und bei Frauen abnimmt. Die stratifizierte Untersuchung des Alterseffektes bzgl. des Geschlechtes zeigt, dass Frauen eine höhere Inanspruchnahme bis zum 69. respektive 74. Lebensjahr vorweisen und sich dieses Verhältnis anschließend umkehrt. Im Vergleich zu deutschen weisen türkische Staatsangehörige eine höhere Inanspruchnahme des Okkultbluttests auf, jedoch eine geringere bei der Koloskopie. Bei beiden Formen der Prävention zeigt sich, dass die Teilnahmeraten geringer ausfallen bei Versicherten ohne Berufsausbildung im Vergleich zu Akademikern.

Obwohl bekannt ist, dass Brustkrebs mit erheblichen ökonomischen Belastungen einhergeht, ist die Evidenzlage in Deutschland eher gering, denn die bereits existierenden Studien berücksichtigen nur wenige Leistungssektoren bzw. stratifizieren nicht anhand der Krankheitslast der Erkrankten. Das Ziel der Studie „Healthcare costs associated with breast cancer in Germany: a claims data analysis“ (Modul 7) bestand daher in der Schätzung der mit Brustkrebs assoziierten Kosten aus Perspektive der GKV, wobei der Schwerpunkt, neben der Erfassung der sektorenspezifischen Kosten, auf der Differenzierung nach unterschiedlichen Behandlungsphasen lag.
Als Grundlage wurden sektorenübergreifende Routinedaten der AOK Bayern verwendet. Nach der Identifikation der Patientinnen, basierend auf den ambulanten sowie stationären ICD Kodierungen, erfolgte die Kostenanalyse mittels eines Kontrollgruppenansatzes. Hierbei wurde ein Matching, im Verhältnis von 1 zu 2, anhand der Kontrollvariablen des Alters, des Geschlechtes und dem Elixhauser-Score für die Komorbiditäten verwendet. Die Definition der Behandlungsphasen erfolgte literaturbasiert in initial, intermediär und terminal, wobei für die Zuordnung der monatlichen Kosten zu einer der jeweiligen Phase die Joinpoint-Regression verwendet wurde. Diese

ermittelt empirisch, wann ein Strukturbruch im Zeitverlauf vorliegt.
Die Resultate belegen die Abhängigkeit und damit einhergehende Variabilität der inkrementellen Kosten von der jeweiligen Behandlungsphase. Für die inzidenten Fälle liegen diese bei durchschnittlich 21.455 € in der initialen, 2.851 € in der intermediären und 33.237 € in der terminalen Phase, so dass die Kostenstruktur einem u-förmigen Verlauf folgt. Auch die sektorenspezifischen Kosten variieren in Abhängigkeit der Behandlungsphase, wobei der stationäre Sektor sowie die Medikation, insbesondere Zytostatika, in den meisten Phasen die größte ökonomische Auswirkung haben.

Mit der Veröffentlichung „Portfolio structure of the German households and the role of insurance and pension entitlements“ (Modul 8) wurde untersucht, welche Faktoren die Assetallokation privater Haushalte in der langen Frist in Deutschland determinieren. Hierbei stand die Vermögensklasse der Versicherungen im Fokus der Auswertungen, da diese zum einen mit einem Sicherheitsmotiv assoziiert wird und zum anderen im Zeitverlauf zahlreichen makroökonomischen Einflüssen unterlegen ist.
Für die Analysen wurde aus unterschiedlichen Quellen eine Längsschnittdatenbank von 1975 bis 2014 generiert. Die Ausgangsbasis bildet ein Datensatz der Deutschen Bank, welcher quartalsweise die Verteilung und Entwicklung deutscher Vermögensanlagen von Privathaushalten beinhaltet, wobei dieser auf acht ausgewählte Anlageklassen aggregiert bzw. reduziert wurde. Diesen wurden anschließend korrespondierende Renditeproxies zugeordnet, welche ebenfalls auf Daten der Deutschen Bank basieren, mit Ausnahme der Anlageklasse der Versicherungsansprüche für die Daten der BaFin verwendet wurden. Zudem wurden acht Kontrollvariablen integriert, um mögliche Einflüsse von demografischen, makroökonomischen und versicherungsspezifischen Bedingungen zu berücksichtigen. Die Modellierung und Schätzung der langfristigen Vermögenselastizitäten, insbesondere zwischen den Versicherungsansprüchen und den weiteren Anlageklassen, erfolgte anhand eines FAIDS.
Die deskriptiven Auswertungen zeigen, dass der Anteil der Versicherungsansprüche im Zeitverlauf zunimmt. Anhand des FAIDS wird aufgezeigt, dass kein signifikanter Einfluss der Versicherungsrendite auf die Vermögensklasse der Versicherungsansprüche vorliegt und eine nahezu proportionale Reaktion des Versicherungsanteils auf Veränderungen des Gesamtvermögens erfolgt. Daraus kann geschlossen werden, dass Sicherheit als Hauptnachfragemotiv für die Anlageklasse gilt und nicht die Renditeoptimierung. Diese These wird zusätzlich dadurch gestützt, dass ein positiver Zusammenhang zwischen dem Anteil der älteren Menschen und dem Versicherungsanteil im Portfolio identifiziert werden konnte.

3 Beantwortung der Forschungsfragen und Ausblick

Wie in Kapitel 1 hergeleitet, nimmt aufgrund der zunehmenden Komplexität des Forschungsprozesses die Bedeutung der Konzeption des Forschungsdesigns zu. Die eingebrachten Module in der vorliegenden kumulativen Dissertation (siehe Kapitel 2) stellen Praxisbeispiele für quantitative Forschungsvorhaben dar und leisten einen Beitrag zur Beurteilung der konzeptionellen und methodischen Herausforderungen sowie der Limitationen. Im Folgenden werden die zentralen Forschungsfragen beantwortet.

1. Wie beeinflusst das Spektrum der Fragestellungen die Auswahl der Datenquellen und die damit einhergehenden Strukturen?

Wie auf Seite 3 erläutert, bilden die äußeren Schichten, welche wiederum durch die Fragestellung determiniert werden, die Rahmenbedingungen für die Auswahl der Datengrundlage. Hierbei können aus den vorliegenden Modulen gemeinsame Aspekte sowie Unterschiede in Abhängigkeit der betrachteten Schicht extrahiert werden.

Die Module 5 - 7 umfassen Fragestellungen aus der Perspektive der GKV und obwohl die jeweiligen Outcomes von Behandlungsarten (Modul 5) über Inanspruchnahmeraten (Modul 6) und krankheitsassoziierten Kosten (Modul 7) ein diversifiziertes Spektrum abbilden, können sie inhaltlich auf den Aspekt der ökonomischen Auswirkungen für die GKV und somit den Kostenträger reduziert werden. Mit der GKV-Perspektive geht einher, dass zum einen das für den Kostenträger relevante Versorgungsgeschehen inklusive ökonomischer Bewertung und zum anderen das gesamte potentielle Versichertenkollektiv, soweit in der Fragestellung definiert, abgebildet werden muss. Basierend auf diesen Annahmen stellen Routinedaten die geeignete Datengrundlage für die Analysen dar, denn diese umfassen sämtliche abgerechneten Leistungen der Versicherten der GKV über die relevanten Leistungssektoren hinweg. Die Patientenperspektive steht hingegen in den Modulen 2 und 4 im Mittelpunkt der Betrachtung, wobei hierfür im Gegensatz zu den Modulen 5 - 7, trotz der übereinstimmenden Perspektive, unterschiedliche Datengrundlagen auf Patientenebene benötigt werden. Die Ermittlung der Effektivität einer Therapie (Modul 2)

erfordert die detaillierte Erfassung von klinischen Daten sowie, um die Effekte quantifizieren zu können, die Existenz einer spezifischen Kontrollgruppe. Hingegen werden zur Untersuchung der Entwicklung der Komorbiditätslast bei einer chronischen Erkrankung im Zeitverlauf (Modul 4) standardisierte Informationen zu den Diagnosen sowie vereinzelte klinische Informationen der im Fokus stehenden chronischen Erkrankung benötigt. Die vorgenannten Kriterien werden im ersten Fall durch klinische Studien und im zweiten Fall durch patientenbezogene Register erfüllt. In den Modulen 1, 3 sowie 8 werden Fragestellungen aus der Perspektive der Gesellschaft erörtert und wie zuvor resultieren aus den variierenden Forschungsgegenständen in Teilen divergierende Datengrundlagen. Sowohl die Ermittlung der Präferenzen von pflegenden Angehörigen (Modul 1) als auch die Erfassung der Lebensqualität von Kindern mit einer seltenen chronischen Erkrankung respektive der damit einhergehenden Ressourcennutzung (Modul 3) erfordern Primärdaten auf Personenebene und Befragungen stellen das geeignete Instrument hierfür dar. Hingegen werden für die ökonomische Bewertung der zuvor genannten Ressourcennutzung einheitliche Kostensätze benötigt, welche auf Basis von Literaturrecherchen und Arzneimitteldatenbanken generiert werden können. Analog hierzu kann anhand äquivalenter Datengrundlagen das Anlegerverhalten im Zeitverlauf (Modul 8) analysiert werden. Hierbei werden Zeitreihen zur Assetallokation sowie der dazugehörigen Renditen benötigt, welche aus Datenbanken von Finanzinstitutionen extrahiert werden können. Ergänzende Informationen zu exogenen Rahmenbedingungen werden anhand von Recherchen selektiert.
Die Annäherung an die Forschungsfrage anhand der Schicht der Perspektive zeigt, dass insbesondere die GKV-Perspektive die Auswahl der Datengrundlage determiniert. Im Gegensatz dazu steht bei Fragestellungen aus der Perspektive des Patienten oder der Gesellschaft ein breites Spektrum von Datenquellen zur Verfügung, welches von der konkreten Ausgestaltung der Fragestellung abhängig ist.

Die vorliegenden Module können zudem anhand der Schicht des Forschungsansatzes betrachtet werden, wobei die Module 2, 7 sowie 8 einem deduktiven und die weiteren Module einem abduktiven Ansatz folgen. Die Wahl des Forschungsansatzes beeinflusst dabei insbesondere die Anforderungen an die Strukturen innerhalb der Datengrundlage respektive den Prozess der Datenerhebung und Aufbereitung. Im Falle des abduktiven Ansatzes ist es viabel alle zur Verfügung stehenden Informationen zu operationalisieren, wobei keine zwingenden Voraussetzungen vorliegen. Um dies zu verdeutlichen wird die Ermittlung der Komorbiditätslast im Zeitverlauf (Modul 4) herangezogen. Bei dieser Studie wurden die vorliegenden Registerdaten zunächst vollständig aufbereitet und deskriptiv analysiert. Basierend auf den Ergebnissen erfolgte die Selektion der Variablen zur Stratifizierung sowie deren Ausgestaltung, die Bestimmung des Untersuchungszeitraumes und die Identifikation der Instrumente zur Operationalisierung der Komorbiditäten. Durch dieses Vorgehen wird ein Trade-off zwischen der Maximierung der Fallzahl sowie Sicherstellung der Validität erreicht und zudem das Spektrum der realisierbaren Ergebnismenge potenziert. Im Gegensatz dazu beschränken sich Untersuchungen, die einem de-

duktiven Ansatz folgen, auf die Analyse der aufgestellten Hypothesen und erfordern im Gegenzug, dass die dazu benötigten Informationen in geeigneter Form verfügbar sind und operationalisiert werden können. Beispielhaft sei an dieser Stelle auf die Analyse des Anlegerverhaltens im Zeitverlauf (Modul 8) verwiesen. In dieser Studie lagen die Daten zur Assetallokation für einen längeren Zeitraum vor, aber aufgrund von limitierter Verfügbarkeit benötigter Informationen war es erforderlich, den Untersuchungszeitraum anzupassen, um die ursprünglichen Hypothesen quantifizieren zu können.

2. Welche methodischen Aspekte ergeben sich aus der Fragestellung und Auswahl der Datengrundlage?

Wie im vorherigen Abschnitt ausgeführt, werden in Abhängigkeit der Fragestellung sowie Perspektive unterschiedliche Datengrundlagen benötigt und damit einhergehend variieren die methodischen Herausforderungen bei der Datenaufbereitung sowie Optionen hinsichtlich der Datenanalyse.

In den Modulen 4 - 7 bilden Register- bzw. Routinedaten den Ausgangspunkt für die Untersuchungen, welche dadurch gekennzeichnet sind, dass diese zwar systematisch erfasst werden, jedoch nicht primär für die Art der hier durchgeführten wissenschaftlichen Analysen. Aufgrund der Nutzung der Daten entgegen ihrem originären Zweck werden Algorithmen zur retrospektiven Identifikation des jeweiligen Studienkollektives benötigt, welche individuell in Abhängigkeit der Fragestellung generiert werden. Zudem liegt die zeitlich eindeutige Zuordnung von Leistungen respektive Ressourcenverbräuchen nicht in allen Sektoren vor und muss, wenn notwendig, approximiert werden. Im Gegensatz dazu basieren die Module 1 - 3 auf Befragungen sowie klinischen Erhebungen, welche spezifisch für die jeweilige Untersuchung erstellt bzw. erhoben werden und somit theoretisch direkt ein geeignetes Studienkollektiv erfassen. Allerdings geht dies mit dem Prozess der Rekrutierung einher und dessen Komplexität wird durch die Ausgestaltung des angestrebten Kollektives definiert. Des Weiteren bedarf es Vorarbeiten für den Aufbau der Befragungsinstrumente respektive Planung des Studiendesigns. Abermals werden im Folgenden exemplarisch Module zur Illustration der vorgenannten Aspekte aufgegriffen. Da die Registerdaten des BeoNet nicht nur Patienten mit der Zielerkrankung umfassen, muss gesichert werden, dass die im Studienkollektiv von Modul 4 enthaltenen Patienten an COPD erkrankt sind. Hierzu wurde zunächst die Existenz einer Dauerdiagnose geprüft und anschließend, ob im folgenden Zeitverlauf mindestens ein ambulanter Arztbesuch mit einer Kodierung von COPD erfolgt. Aufgrund der fehlenden Angaben zum Versichertenstatus wurden des Weiteren die Einträge sämtlicher integrierter Sektoren herangezogen, um die Zeitspanne der Beobachtungsdauer je Patient zu approximieren. Die länderübergreifende Analyse einer chronischen Erkrankung bei Jugendlichen (Modul 3) verdeutlicht die Herausforderungen bei der Rekrutierung. Obwohl die Kontaktaufnahme mittels Patientenorganisationen über 20 Monate erfolgte, konnten nur

geringe Fallzahlen in die Studie eingeschlossen werden, welche sich zudem heterogen über die inkludierten Länder verteilen. Die Komplexität der Erstellung eines Fragebogens zeigt sich bei der Untersuchung der Präferenzen von pflegenden Angehörigen (Modul 1). Hierzu wurden zunächst eine systematische Literaturrecherche sowie semi-strukturierte Interviews durchgeführt und auf den Ergebnissen basierend der Fragebogen generiert, welcher anschließend mittels einer Pilotstichprobe validiert und finalisiert wurde. Die Module 2, 3 sowie 8 inkludieren öffentliche Statistiken, Datenbanken und Literaturrecherchen inklusive daraus abgeleiteter Parameter. Bei der Verwendung dieser Datengrundlagen besteht insbesondere die Herausforderung der Selektion geeigneter Variablen, welches als Adäquationsproblem bezeichnet wird. Wiederum wird auf die Analyse des Anlegerverhaltens im Zeitverlauf (Modul 8) verwiesen, bei der wie zuvor dargestellt, für jede der Anlageklassen ein Renditeparameter benötigt wird und hierfür unterschiedliche Optionen zur Verfügung stehen. Beispielhaft wurden für die Klasse der Investmentfonds drei Renditeparameter inkludiert, welche anhand des Volumens innerhalb der Anlageklasse aggregiert wurden.
Die vorherigen Ausführungen verdeutlichen, dass die Auswahl der Datengrundlage insbesondere den Teilprozess der Datenerhebung sowie Datenaufbereitung definiert. Hierbei bedingen Primärdaten eine verstärkte Arbeitsintensität bei der Datenerhebung, wohingegen Sekundärdaten mit einem erhöhten Aufwand bei der Datenaufbereitung einhergehen.

Die divergierenden Datengrundlagen und Zielstellungen resultieren in der Anwendung eines breiten Methodenspektrums. In den Modulen 3 und 4 steht die Ermittlung von Parametern sowie vergleichende Beschreibung im Mittelpunkt der Betrachtung und dies kann anhand von deskriptiven Analysen und Hypothesentests realisiert werden. Im Gegensatz dazu werden in den weiteren Modulen potentielle Einflussfaktoren untersucht und dies bedingt den Einsatz von Regressionsmethoden, wobei die Ausgestaltung von der Zielstellung abhängig ist. Die Untersuchung von Behandlungsarten respektive Inanspruchnahmeraten (Module 5 und 6) kann beispielweise anhand der logistischen Regression erfolgen, wohingegen die Analyse der zeitlichen Dimension die Verwendung komplexer Methoden impliziert, wie dem Kaplan-Meier-Schätzer (Modul 2) oder der Joinpoint-Regression (Modul 7). Hierbei gilt es jedoch die spezifischen Einschränkungen aufgrund der Datengrundlagen zu beachten.

3. Welche Limitationen resultieren aus den verwendeten Datengrundlagen und wie können diese adressiert werden?

Die in der vorliegenden Dissertation integrierten Module basieren auf einer Vielfalt an Datengrundlagen, wie in den vorherigen Kapiteln dargestellt. Mit jeder Quellenart gehen Limitationen einher, welche sowohl systematisch als auch projektspezifisch bedingt sein können. Im Folgenden werden exemplarische Beispiele aufgegriffen und die Konsequenzen respektive Lösungsansätze ausgeführt.

Die Module 1 - 3 beruhen auf Primärdaten und wie zuvor dargestellt, werden diese spezifisch für die jeweilige Fragestellung generiert und erreichen dadurch einen hohen Anpassungsgrad. Mit dieser Vorgehensweise gehen jedoch die Problematik von geringen Fallzahlen sowie der potentiell eingeschränkten Generalisierbarkeit der Ergebnisse einher und diese wurden anhand divergierender Ansätze berücksichtigt. Bei der Ermittlung der Determinanten von informeller Pflege (Modul 1) war es das Ziel die Allgemeinbevölkerung abzubilden. Um dies zu erreichen, wurde durch die kooperierende Krankenkasse eine geschichtete Zufallsstichprobe für die Befragung selektiert, welche die Struktur ausgewählter soziodemografischer Merkmale der deutschen Bevölkerung repräsentiert. Die Ergebnisse hinsichtlich der Effektivität einer Chemotherapie (Modul 2) basieren auf einer klinischen Studie mit 90 Teilnehmern, welche aufgrund des Einschlusses in die Studie einer charakteristischen Selektion unterliegen. Daher wurde eine Metaanalyse inkludiert, um die ermittelten Effekte zu validieren. Die Nutzung von Routinedaten (Module 5 - 7) impliziert eine Vielzahl an Limitationen. Beispielhaft können das Fehlen klinischer Parameter, die nicht eindeutige zeitliche Zuordnung von Leistungen im ambulanten Sektor oder die Unsicherheit hinsichtlich der Validität der Diagnosen genannt werden.[10] Bei der Ermittlung von Einflussfaktoren auf die Behandlungsart (Modul 5) ist die Berücksichtigung des Schweregrades notwendig, welche jedoch aufgrund der fehlenden klinischen Parameter nicht direkt möglich ist. Daher wurde das Vorliegen relevanter Komorbiditäten identifiziert und als Kontrollvariable inkludiert, um den Schweregrad zu approximieren. Die Anwendung der Joinpoint-Regression zur Differenzierung der Kosten nach Behandlungsphasen (Modul 7) erfordert, dass die Daten als Zeitreihe vorliegen. Die bereitgestellten ambulanten Kosten lagen jedoch lediglich auf Jahresbasis vor, so dass diese anhand einer Gleichverteilung auf Monatsbasis transformiert wurden. In den Modulen 4 und 8 bestehen die Limitationen insbesondere aufgrund der gewählten Strukturen der Datengrundlage. Um die Komorbiditätslast im Zeitverlauf (Modul 4) zu untersuchen, ist es notwendig, dass Informationen vorliegen, ob der Patient durchgängig beobachtet werden kann. Die Registerdaten beinhalten zwar sämtliche Einträge der elektronischen Patientenakte, jedoch keine Informationen zum Versichertenstatus oder Verknüpfungen zwischen den integrierten Praxen. Daher wurde aus allen inkludierten Daten je Patient das erste sowie letzte kodierte Datum extrahiert, um damit die Beobachtungsdauer zu approximieren. Die Analyse des Anlegerverhaltens im Zeitverlauf (Modul 8) erforderte den Aufbau einer Datenbank von Zeitreihen. Aufgrund des 40-jährigen Untersuchungszeitraumes und damit einhergehenden Änderungen in den Systematiken der Erfassung lagen nicht für alle Anlageklassen durchgängige Renditeproxies vor. Daher wurden Extrapolationen angewendet, um Strukturbrüche zu vermeiden und die Konsistenz der Analysen zu gewährleisten.

Zusammenfassend zeigen die vorliegenden Beiträge, dass bei der Konzeption des Forschungsdesigns ein breites Spektrum an Optionen und damit einhergehenden Kombinationsmöglichkeiten existiert. Dabei steht im Wesentlichen die Auswahl der Datengrundlage im Fokus des Pla-

10 Vgl. Neubauer u. a. 2017 für einen umfangreichen Überblick der Limitationen von Routinedaten.

nungsprozesses, denn diese determiniert die methodischen Aspekte und somit die potentiellen Anwendungsmöglichkeiten der Analysen. Hierbei verfügen alle dargestellten Datengrundlagen über spezifische Profile hinsichtlich ihrer Stärken sowie Schwächen, wobei insbesondere die jeweiligen Limitationen adressiert werden müssen, um die Validität und Aussagekraft der Untersuchungen zu gewährleisten. Wie exemplarisch in Modul 2 aufgezeigt, kann ein Lösungsansatz in der Implementierung von Mixed-Methods-Ansätzen liegen. Diese vereinen unterschiedliche Datenquellen und/oder Methodiken und bieten daher die Chance anhand divergierender Potentiale die Limitationen auszugleichen. Beispielhaft können Primärdaten generiert werden, um explorativ ein Feld zu erschließen, bevor mittels Sekundärdaten die Generalisierbarkeit validiert wird. Konträr dazu könnten basierend auf Sekundärdaten allgemeine Hypothesen abgeleitet und durch die anschließende Erhebung von Primärdaten ein vertieftes Verständnis der kausalen Zusammenhänge generiert werden. Im Bereich der gesundheitsökonomischen Forschung zeigt die Betrachtung der vom Innovationsfonds geförderten Projekte die zunehmende Verbreitung der Mixed-Methods-Ansätze.

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Module

Module

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1	Willingness to provide informal care to older adults in Germany: a discrete choice experiment	B	0,87	5,271
2	PICCA study: panitumumab in combination with cisplatin/gemcitabine chemotherapy in KRAS wild-type patients with biliary cancer - a randomised biomarker-driven clinical phase II AIO study	n. g.	2,87	10,002
3	Social/economic costs and health-related quality of life in patients with juvenile idiopathic arthritis in Europe	B	0,87	5,271
4	Age- and gender-based comorbidity categories in general practitioner and pulmonology patients with COPD	n. g.	0,65	3,289
5	Pediatric solid organ injury - frequency of abdominal imaging is determined by the treating department	n. g.	0,47	1,817
6	Determinants of colorectal cancer screening in Germany: a claims data analysis	n. g.	0,25	1,769
7	Healthcare costs associated with breast cancer in Germany: a claims data analysis	B	0,87	5,271
8	Portfolio structure of the German households and the role of insurance and pension entitlements	C	0,15	n. g.

SJR – Scimago Journal & Country Rank 2021; Quelle: https://www.scimagojr.com; Stand: September 2022

JIF – Journal Impact Factor 2021; Quelle: https://jcr.clarivate.com/jcr/home; Stand: September 2022

n. g. – nicht gelistet

Modul 1

Willingness to provide informal care to older adults in Germany: a discrete choice experiment

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ORIGINAL PAPER

Willingness to provide informal care to older adults in Germany: a discrete choice experiment

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Abstract
As the German population is continually aging and the majority of older adults still wish to 'age in place', the need for informal care provided by family and friends will correspondingly continue to increase. In addition, while the need for formal (professional) care services is also likely to increase, the supply already does not meet the demand in Germany today. The aim of our study is the elicitation of people's willingness to provide informal care by means of a discrete choice experiment. The self-complete postal survey was disseminated to a random sample of the German general population in Lower Saxony. Data cleansing resulted in a final sample size of 280 participants. A conditional logit and a latent class model were estimated. All attributes were judged as highly relevant by the respondents. The results revealed that an increase in the care hours per day had the greatest negative impact overall on the willingness to provide informal care in our sample. The marginal willingness-to-accept for 1 h of informal care was €14.54 when having to provide informal care for 8 h in reference to 2 h per day. This value is considerably higher than the national minimum wage of €9.82. A three-class latent class model revealed preference heterogeneity. While a monetary compensation is often discussed to increase the willingness and availability of informal care in a country, our results show that this statement could not be generalized within our entire sample.

Keywords Discrete choice experiment · Elderly care · Older adult care · Long-term care · Preferences · Willingness

JEL Classification C35 · I18 · J10 · J14

Introduction

Long-term care (LTC) encompasses a variety of services that aim to manage and further delay the functional decline of people with a care dependency by, among others, alleviating pain, assisting with activities of daily living, and ensuring independent living [1]. In Germany, a mandatory LTC insurance was introduced in 1995 to ensure access to LTC services for the entire population. Entitlement to LTC insurance benefits is based on a calculated care dependency grade. For this purpose, a new instrument was introduced in 2017 that uses six modules to determine the need for care of each person on a scale from 0 to 100. The modules and corresponding weights are as follows: 1. Mobility (10%), 2. Cognitive and communicative abilities or 3. Behaviour and psychiatric problems (15%), 4. Self-care (40%), 5. Dealing with requirements due to illness or therapy (20%), and 6. Organisation of everyday life and social contacts (15%). Each module consists of different items for which points are given. In the end, item points are added within each module and incorporated in the final score depending upon the mentioned module weights. The final score is then translated to one of the five care grades. A higher care grade translates to a more severe care dependency and therefore also a higher available budget [2, 3]. Recent statistics show that of the 4.1 million care-dependent Germans in 2019, 80% were cared for at home. Of these, 2.33 million (56%) were cared for exclusively by family members, neighbors, or friends. This type of care is also referred to as informal care and constitutes an important pillar of the LTC system in Germany and many other countries around the world [4].

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As the German population is continually aging and the majority of older adults still wish to 'age in place', the need for informal care will correspondingly continue to increase. In addition, while the need for home- and community-based services (HCBS) is also likely to increase, the supply already does not meet the demand in Germany today, due to a lack of qualified professionals and care infrastructure [5]. Therefore, recent care reforms have explicitly tried to strengthen home-based care and support informal caregivers, while many still criticize its implementation and reach. Nevertheless, current care systems rely on people's willingness to provide informal care, as the professional care structures and workforce in place are not able to provide care to the increasing number of care-dependent older adults. When it comes to understanding the reasons for people to take on the role of an informal caregiver, arguments are complex and still not well understood [6]. On the one hand, many studies have highlighted the immense burden informal caregivers' face in many life settings. First, studies have stressed the toll caregiving can have on a caregiver's physical and mental health, including back pain, sleep deprivation, and depression [7]. Second, a study by Geyer (2016) has found out that caregivers that provided care for more than 1 h a day needed to reduce their working hours by 5–8 h per week [8]. In addition, re-entering the workforce as full-time employees following the informal caregiving situation is made more difficult [9]. Therefore, informal caregiving can lead to financial hardship [10]. Thirdly, many informal caregivers report that caregiving places increased pressure on their relationships to friends and family. This in turn adds pressure on the informal caregiver, and can lead to self-isolation in some cases and may influence quality of life [11]. On the other hand, studies have also shown that informal caregiving can confer positive psychological effects, which in turn can protect caregivers from experiencing high levels of stress. More specifically, studies report increased levels of resilience, self-confidence, and a sense of meaning [12, 13].

From an economic perspective, the decision to provide informal care is only rational if the utility or value outweighs its costs or burden. Costs or burden can be measured with different methods such as out-of-pocket expenses, time input, or instruments measuring the subjective burden or (health-related) quality of life. Quality of life and well-being instruments can also be used to measure the value of informal care [14]. Several theories try to explain the decision-making process. In an altruistic model, the hypothesis is that the selfless (informal) caregiver draws utility from the well-being of the person in need of care [15]. Cox and Stark (1996) have proposed a different theory, known as the demonstration effect. In this theory, adults with own children are incentivised to provide informal care to their older parents in hopes that their own children internalize the behavior and in turn care for them in the future. Other economic models try to explain informal caregiving using strategic exchanges between the two parties involved. Such exchanges can be in the form of financial incentives or money transfers (e.g., inheritance) between parents and children [16]. To be able to include informal care in economic evaluations, informal care needs to be valued either in terms of costs or carer effects. Monetary valuations of informal care can be done by for instance the opportunity cost method, proxy good method, contingent valuation, conjoint analysis, or discrete choice experiment (DCE), as has been applied in this study [14].

The study on LTC preferences in the field of older adult care has seen an increase over the last few years, especially by means of quantitative stated preference methods, such as DCE, contingent valuation, or best–worst scaling [17]. In the field of LTC, such methods have been used to elicit preferences for different LTC options, the suitability of different LTC settings for hypothetical patient outcomes, as well as the design and structure of specific LTC services such as home-based and community-based services or LTC facilities. Preferences can serve as an important indication to better tailor services to the needs, expectations, and wishes of its consumers. Among choice-based techniques in the field of older adult care, DCE were most often applied and enabled a ranking of the importance of the chosen attributes as well as an assessment on trade-offs respondents were willing to make. Specifically, in the field of informal care, most often contingent valuation methods were applied to explore the value of informal care by estimating the willingness-to-pay (WTP) for a reduction of 1 h in informal caregiving time [18–21]. In one of these studies, willingness-to-accept (WTA) values for having to provide one additional hour of informal care were additionally estimated by informal caregivers in China [21]. In a study by Mentzakis et al. (2011), a DCE was used to value various informal care tasks by informal caregivers in Scotland [22].

To date, one other DCE has been conducted in Germany in the field of LTC, however, focusing on investigating people's preferences for home- and community-based services [23]. The aim of our study is the elicitation of people's willingness to provide informal care in Germany by means of a DCE. The use of this methodology not only enables an inquiry into people's willingness to care but also an assessment of what people value as most important and would be willing to trade-off. As national governments need to establish sustainable and affordable LTC systems, knowledge on people's willingness to care as well as their trade-offs can add an important puzzle piece for the planning of services as well as support needed to enable more people to take on the role of caregiver.

Methods

DCEs are increasingly applied in health economics to elicit and quantify people's preferences. DCEs involve asking respondents to choose between two or more attribute-based alternatives. The underlying assumption of any DCE is that healthcare interventions and products can be decomposed and described by a set of characteristics (attributes) and that people value these differently depending on the levels of each attribute. The discrete choices made by respondents are then analyzed with different regression models and allow the estimation of the relative importance (utility) of each attribute [24, 25].

Attributes and levels

Results from a systematic literature review of the scientific databases PubMed, Scopus, and Dimdi [26] and 33 semi-structured qualitative interviews [6, 27] were used to identify the most relevant attributes and corresponding levels. While the type and severity of a care dependency as well as the (relationship to) the care-dependent person are important determinants for a person's willingness to provide care [6], we decided to solely focus on relevant attributes that describe informal caregiving situations in the DCE. Five quantitative attributes with three levels each were identified. A sufficiently wide-level range was classified as is recommended by the literature [28]. The chosen attributes, levels, and the description of each attribute can be found in Table 1. When choosing attributes and levels, compiled choice sets needed to be realistic but also force respondents to trade-off between the levels of each alternative and choose one of the two options. Therefore, 8 h per day in care time was for example chosen as an equivalent to a full-time working day. 0€ per hour of informal care, meaning no financial compensation, was chosen to exemplify the intrinsic willingness to provide care without any monetary compensation. In these scenarios it can be assumed that motivation exists on its own, for instance motivated by love or a sense of obligation for taking care of the relative in need.

The understanding of the attributes and levels as well as the entire questionnaire was piloted in a random sample of the general population ($n = 30$) in a step-wise procedure, meaning that the questionnaire was altered following participant comments and then tested again. The responses led to a series of wording alterations to simplify the questionnaire; however, no attributes or levels had to be changed.

Experimental design

A two-alternative forced-choice design was created with the software SAS [29]. As the full factorial design would result in 243 (Level Attribute = 3^5) possible attribute-level combinations, a fractional factorial design with 54 choice sets was created and blocked into six questionnaire versions with nine choice sets each to reduce respondents' burden. All of these choice sets were checked for plausibility, assigned to the blocks at random and it was ensured that there were no correlated attributes within versions. Generic alternatives (situation A vs. B) were chosen. The fractional factorial design was constructed using the %MktEx macro to make a candidate set of alternatives, followed by the %ChoicEff macro to create an efficient experimental design. The %ChoicEff macro uses a modified Fedorov algorithm, in which all design possibilities are considered and swapped out if the swap improves the D-efficiency [29]. A detailed explanation of all macros can be found in the book by Kuhfeld [29]. A

Table 1 DCE attributes and levels

Attribute	Attribute description	Levels
Expected period of caregiving (duration of care)	The period of time the caregiver would care for and/or look after the person in need of care	6 months 2 years 5 years
Care time (hours per day)	The amount of time (hours per day) the caregiver would provide care and/or supervise the person in need of care at home (e.g., personal care, household tasks, doctor visits etc.)	2 h per day 5 h per day 8 h per day
Formal care services (frequency per week)	The frequency of professional support that is additionally available to the caregiver (e.g., outpatient care services can assist with personal care or counselors can help with any open questions) A visit lasts about 30 min	None 3–4 times a week Daily
Respite (weeks per year)	The number of weeks a year that are available to the caregiver for a variety of respite options. During this time period, professionals care for the individual in need (e.g., during vacation)	None 3 weeks per year 6 weeks per year
Monetary compensation (€ per hour)	A wage replacement benefit (net) at the personal disposal of the caregiver. Paid as a financial compensation per hour for the care provided (in addition to the existing cash benefits by the LTC insurance in Germany)	€0 per hour €6 per hour €12 per hour

priori attribute coefficients were set to zero in the design. The design with 54 choice sets allowed for the clean estimation of main effects and all two-way interaction effects. In the design construction, the criteria 'identification' and 'efficiency' were explicitly considered as is recommended by the literature [28]. Identification, meaning that effects can be estimated independently, was determined by the structure of the inverse of the variance–covariance matrix of the parameter estimates. Efficiency, meaning the precision by which effects are estimated, was determined by improving the D-efficiency. The D-efficiency is a standard measure of goodness that can be used to compare the specific experimental designs that are created with the software SAS [29].

Study population and sample size

The mode of the data collection was a self-complete postal survey. The DCE questionnaire was disseminated to a stratified random sample of 4000 individuals of the German general population via a statutory health insurance (AOK Lower Saxony). The AOK Lower Saxony is the largest health insurance company in its region with a representative structure of insured compared to the entire German population in terms of socio-demographics such as age and sex. Differences were only observed in terms of education and occupation; in particular, the proportion of people with a university degree and higher job complexity was lower among AOK insured compared to the entire Lower Saxony population [30]. A reminder postcard was not sent. The population data from the end of 2017 were used as the data basis to draw a representative sample of the general population by the respective age and gender proportions between 18 and 65 years [31]. We used the equation by Johnson and Orme (2003) to determine the minimum required sample size of 250 respondents [32]. The formula is shown below, where t is the number of choice tasks, a is the number of alternatives, and c is the largest number of levels for any of the attributes or the largest product of levels of any two attributes [32]

$$N > \frac{500c}{(t * a)}$$

The questionnaire

The questionnaire was printed in a book format to enable easier readability and was a total of ten pages long. Respondents were given the contact information of the lead author to be able to ask questions. The first page contained a concise participant information including the necessary data protection clarifications. The following two pages enclosed instructions on how to complete the questionnaire, including a table of the attributes and levels as well as an example choice set (see Fig. 1). Respondents were asked to imagine a close relative in need of care. This person was able to be cared for at home and medical or nursing tasks (e.g., wound care) would be cared for professionally. The respondents were then shown an example choice task with two care situations (A vs. B) and it was underlined that no wrong answers were possible, as this was a subjective opinion. The main research question asked to the respondents was: "Under what conditions are you willing to provide care to a close relative? What is important to you personally?". Subsequently, respondents were asked to choose the preferred care situation in the following nine choice tasks. The questionnaire blocks, meaning the respective DCE choice tasks, were presented to respondents in a random order to ensure that order bias was not systematic across the sample. After the DCE tasks, 19 additional questions were posed regarding age, gender, current health status, living and family situation, income, education, previous caregiving experience, and a number of attitudinal questions regarding the person's willingness to care (e.g., willingness to reduce working hours). At the end of the questionnaire, a blank space was provided for further comments of the respondents.

Fig. 1 Example of a DCE choice set

Attributes (characteristics)	Situation A	Situation B
Expected period of caregiving (duration of care)	2 years	5 years
Care time (hours per day)	2 hours per day	5 hours per day
Formal care services (frequency per week)	Daily	None
Respite (weeks per year)	6 weeks per year	3 weeks per year
Monetary compensation (€ per hour)	12 € per hour	6 € per hour
In which situation would you prefer to provide care?	**Situation A:** ❒	**Situation B:** ❒

Data analysis and interpretation

Socio-demographic data were analyzed using descriptive methods following data cleansing. Except for mean age, all other variables were depicted as the absolute number of cases and respective percentages in reference to the total sample. The analysis of the collected choice data is theoretically based on Lancaster's characteristics theory of demand [33] and random utility theory [34]. More specifically, choice data are analyzed on the premise that each individual will choose the alternative (here: care situation) that provides the highest utility to the individual. The utility U of individual q choosing alternative i can be decomposed into a deterministic part V and a non-explainable or random component ε and written as [28]

$$U_{iq} = V_{iq} + \varepsilon_{iq}$$

For the multivariate analyses, a conditional logit model (CLM) and a latent class model (LCM) were used. For the CLM, we assumed that error terms are independently distributed with a type 1 extreme value (Gumbel) distribution. Models were estimated without and with two-way interaction effects. The probability of choosing one alternative i over the other is given by

$$P_{iq} = \frac{\exp(V_{iq})}{\sum_{j=1}^{J}\exp(V_{jq})}$$

All attribute levels were dummy-variable coded, except for the cost attribute in the CLM. Therefore, coefficients were interpreted as deviations from the reference level that was defined beforehand (except for the cost attribute). Positive coefficients >0 indicate a preference for that attribute level, while negative coefficients <0 indicate a non-preference for that attribute level. The coefficients were assumed to be statistically significant at a p value of ≤ 0.05. Since the DCE included the cost attribute "monetary compensation", we additionally calculated the marginal WTA (MWTA) for attribute levels in comparison to the reference levels using

$$\mathrm{MWTA}_{\mathrm{attribute}} = -\left(\frac{\beta_{\mathrm{attribute}}}{\beta_{\mathrm{costattribute}}}\right)$$

Further information on the theoretical foundation of DCE can be found elsewhere [22, 28]. In the LCM, we were able to include determining factors (e.g., sex or age) that influenced the choices made in the DCE between care situation A and B (dependent variable). Thus, the LCM allowed an estimation of the importance of DCE attributes for each class as well as the variables that determined class membership to estimate preference heterogeneity. The probability of individual q choosing alternative i in the depicted situation t depending on falling within the class c is written as follows:

$$P_{iqt|c} = \frac{\exp(x_{iqt}\beta_c)}{\sum_{j=1}^{J}\exp(x_{jqt}\beta_c)}$$

Models were tested with altering number of classes and different independent variables. Correlations between independent variables were tested using Spearman rank, polychoric, and Cramer's V correlation measures. As highly correlated independent variables weaken the statistical and explanatory power of our LCM, these were removed. Study population characteristics were included in the segmentation models from the beginning and not analyzed post-classification. For all multivariate analyses, Akaike (AIC) and Bayesian information criteria (BIC), log-likelihood as well as pseudo-R-squared values were used to determine the final model. In particular, when comparing models, the values AIC and BIC should be minimized, while the pseudo-R-squared value should be maximized. All analyses were conducted with R statistics 4.0.4, using the package "survival" for the CLM and the package "lcmm" for the LCM [35].

Results

Descriptive statistics

A total of 324 questionnaires were returned (response rate: 8.1%). Of the 324 questionnaires, 44 had missing values with regard to the DCE choice tasks as well as socio-demographic data and were therefore excluded from the analysis. The distribution of age and sex did not significantly differ between the included and the excluded participants, and the missing data were not specific to any one task or socio-demographic question. Socio-demographic data were analyzed descriptively and are shown in Table 2. A considerably higher proportion of women participated in our study (71%). On average, respondents were around 45 years old. The majority of included participants were married or in a permanent relationship (66%) and had children (68%). Around two-thirds of the sample had a high education (at least a completed vocational training or university entrance qualification) and approximately 80% were full- or part-time employed. Almost 60% of the participants had a household income of 1500€ and higher at their disposal. The majority of respondents reported a very good or good health status (65%). Having siblings and the fact whether or not the respondent's parents were still alive were additionally reported as two factors potentially influencing the reported willingness to provide informal care. 59% of the sample had personal care experiences. This refers to experiences either in organizing informal and/or home-based care services or providing informal care themselves (either alone or with support).

Table 2 Characteristics of included participants ($n = 280$)

	$N = 280$
Sex	
Male	81 (29%)
Female	199 (71%)
Mean age (median)	45.2 (49.00)
Marital status	
Single	67 (24%)
Married or in serious relationship	184 (66%)
Widowed	7 (3%)
Divorced or separated	22 (8%)
Having children	
Yes	189 (68%)
No	91 (33%)
Having siblings	
Yes	259 (93%)
No	21 (8%)
Education	
Low	103 (37%)
High	177 (63%)
Current employment status	
Part-time employment	80 (29%)
Full-time employment	133 (48%)
Unemployed	45 (16%)
Retired	22 (8%)
Household income	
Prefer not to say	26 (9%)
Below 500€ up to 1500€	92 (33%)
1500€ up to 3000€	107 (38%)
3000€ to 5000€ and above	55 (20%)
Are your parents still alive?	
Yes, both	134 (48%)
One parent is deceased	84 (30%)
No	62 (22%)
Health status	
Very good	49 (18%)
Good	132 (47%)
Satisfactory	65 (23%)
Less good	27 (10%)
Bad	7 (3%)
Care experience	
Yes	165 (59%)
None	115 (41%)

Multivariate analyses

Conditional logit model

Table 3 shows the main effect coefficients for the CLM and all five attributes were statistically significant to the entire sample. An increase in the expected period of caregiving (duration) as well as the care time per day had a negative impact on respondents' willingness to care, while the remaining three attributes had a positive impact. The largest negative coefficient was found for having to provide care for 8 h a day in reference to 2 h a day. This indicates that for the entire sample, an increase in the care hours per day reduced willingness to provide informal care. The largest positive coefficient was found for having formal services provide care three to four times a week to the person in need. This indicates that having formal care assistance was very important to the entire sample and increased their willingness to provide care. An increase in the formal care services correspondingly increased the odds of respondents being willing to provide care by the factor of 3.3. The MWTA for 1 h of informal care was €8.77 when having to provide care for 5 h a day and €14.54 when having to provide 8 h of care a day, always in reference to providing care for 2 h a day. For an increase in the expected duration of caregiving, respondents were willing to care for an expected period of 2 years when receiving a minimum of €3.34 of monetary compensation per hour and a minimum of €9.41 for an expected period of 5 years. Negative WTA values indicate that for our entire sample, these attributes or characteristics (formal care services and respite) would result in respondents being willing to forego a monetary compensation or theoretically even additionally pay for these services.

While interaction models are not often applied in the literature due to its complexity, we additionally calculated a CLM with main effects as well as all two-way interaction effects. Results are shown in Table 1 in the supplementary material. Similar to the findings of Nicolet et al. (2018), we found that including all two-way interaction effects slightly improved model fit [36]. In the interaction model, it is important to refrain from interpreting isolated main effects from interaction effects, as such interpretations can be misleading. Additionally, only statistically significant effects can be interpreted. While the main effects for daily formal care services and respite are no longer statistically significant on their own, the interaction effects indicate a very high (positive) impact on peoples' willingness to provide informal care when care situations included daily formal assistance and respite.

Latent class model

Models are estimated with different number of classes (2–5) and compared with reference to three goodness-of-fit measures (log-likelihood, AIC, and BIC). A particular emphasis is placed on the BIC when comparing LCMs, as is recommended in the literature [37]. Preference heterogeneity was investigated in reference to seven independent variables by means of the LCM. Based on BIC, a three-class LCM was selected. Class 1 comprised 40% of our sample, class 2

Table 3 Conditional logit model (main effects only)

Attributes/levels	Coefficient	OR	95% CI	SE	*P* value	MWTA (€)
Duration (Ref: 6 months)						
2 years	–0.37	0.69	(–0.53; –0.22)	0.08	0.00*	3.34
5 years	–1.06	0.35	(–1.21; –0.90)	0.08	0.00*	9.41
Care time (Ref: 2 h/day)						
5 h/day	–0.99	0.37	(–1.14; –0.83)	0.08	0.00*	8.77
8 h/day	–1.63	0.20	(–1.79; –1.48)	0.08	0.00*	14.54
Formal care services (Ref: none)						
3–4 times/week	1.20	3.31	(1.05; 1.35)	0.08	0.00*	–10.67
Daily	1.14	3.12	(0.98; 1.30)	0.08	0.00*	–10.14
Respite (Ref: none)						
3 weeks/year	0.58	1.78	(0.42; 0.73)	0.08	0.00*	–5.13
6 weeks/year	0.50	1.65	(0.35; 0.66)	0.08	0.00*	–4.48
Monetary compensation (€/h)	0.11	1.12	(0.60; 0.75)	0.01	0.00*	
Log likelihood	–2406.9					
Pseudo-R^2	0.19873					
AIC	4831.8					
BIC	4884.2					
No of observations	5030					
No of coefficients	9					

OR odds ratio; *AIC* akaike information criteria; *BIC* bayesian information criteria; *SE* standard error; *MWTA* marginal willingness to accept (€/h)

*$p < 0.05$

roughly 24%, and class 3 approximately 36%. Table 4 presents an overview of the preference data separated for the three classes.

Class 1 ($n = 112$) showed a strong dislike for an increase in the care time per day compared to the remaining two classes. Having to provide care for 8 h compared to 2 h a day had the greatest impact on respondents' willingness to care ($\beta = -1.82714$, $p < 0.001$) in class 1. An increase in the expected period of caregiving (duration) was also valued negatively, while formal care services, respite and 12€ of monetary compensation per hour had a positive impact on the willingness to care of respondents in class 1. In comparison, for class 2 ($n = 66$), an increase in the expected period of caregiving had the greatest (negative) impact on their willingness to provide informal care, in particular 5 years in comparison to 6 months ($\beta = -1.30519$, $p < 0.001$). A care time of 5 h in comparison to 2 h a day was valued positively by the respondents of class 2, along with formal care services and respite. Daily formal care services had the greatest positive impact on their willingness to care ($\beta = 0.96246$, $p < 0.001$). Monetary compensation had no significant impact on respondents' decision-making in class 2. Class 3 ($n = 102$) was the only group that valued an expected period of caregiving of 5 years positively ($\beta = 0.13638$, $p < 0.05$). Having to provide care for 8 h a day had a negative impact on the group's willingness to provide care ($\beta = -0.37385$, $p < 0.001$). The most important attribute for class 3 was the monetary compensation. Receiving 12€ per hour of informal care had the greatest positive impact on their willingness to care ($\beta = 1.66179$, $p < 0.001$).

As we included several independent variables in the segmentation process of the LCM, class membership effects could additionally be estimated. The differences between class 1 and 2 in reference to the included seven independent variables are shown in Table 5 (referenced against class 3).

Respondents in class 1 and 2 did not significantly differ in terms of age and health status in comparison to participants in class 3. Class 2 is comprised of a significantly greater proportion of women ($\beta = -1.37013$, $p < 0.05$) and fewer people with care experience compared to class 3 ($\beta = -0.92833$, $p < 0.05$). Both classes had a lower proportion of individuals that found it very important (Likert scale: 5) for family members to take care of themselves in case of a care dependency compared to class 3 (class 1: $\beta = -1.24867$, $p < 0.05$, class 2: $\beta = -1.99153$, $p < 0.05$). Class 2 additionally had a significantly higher proportion of respondents with a high household income in comparison to class 3 ($\beta = 1.23153$, $p < 0.05$). The precise socio-demographic structure of all three classes is shown in Table 2 in the supplementary material with the absolute numbers as well as the probabilities per class.

Table 4 Latent class model (attribute preferences)

Attribute/level	Class 1 ($n=112$, 40%)			Class 2 ($n=66$, 23.57%)			Class 3 ($n=102$, 36.43%)		
	Coefficient	SE	*P* value	Coefficient	SE	*P* value	Coefficient	SE	*P* value
Intercept	Not estimated			–1.03	0.18	0.00*	–2.27	0.12	0.00*
Duration (Ref: 6 months)									
2 years	–0.20	0.06	0.00*	–0.59	0.09	0.00*	0.10	0.07	0.12
5 years	–0.68	0.06	0.00*	–1.31	0.10	0.00*	0.14	0.06	0.03*
Care time (Ref: 2 h/day)									
5 h/day	–1.21	0.06	0.00*	0.23	0.10	0.02*	–0.25	0.06	0.00*
8 h/day	–1.83	0.07	0.00*	–0.13	0.09	0.12	–0.37	0.07	0.00*
Formal care services (Ref: none)									
3–4 times/week	0.58	0.06	0.00*	0.68	0.10	0.00*	0.71	0.07	0.00*
Daily	0.20	0.06	0.00*	0.96	0.10	0.00*	0.72	0.07	0.00*
Respite (Ref: none)									
3 weeks/year	0.19	0.06	0.00*	0.30	0.10	0.00*	0.27	0.07	0.00*
6 weeks/year	0.20	0.06	0.00*	0.21	0.09	0.02*	0.41	0.06	0.00*
Monetary compensation (Ref: 0€/h)									
6€/h	0.08	0.06	0.19	0.16	0.09	0.08	0.93	0.07	0.00*
12€/h	0.23	0.06	0.00*	0.10	0.09	0.28	1.66	0.08	0.00*
Log-likelihood	–2617.07								
AIC	5376.14								
BIC	5634.21								
Number of parameters	71								

*$p<0.05$

Table 5 Class membership effects for the latent class model (fixed effects)

	Class 1 ($n=112$, 40%)			Class 2 ($n=66$, 23.57%)		
	Coefficient	SE	*P* value	Coefficient	SE	*P* value
Intercept	0.20	0.66	0.77	0.36	0.80	0.65
Sex (Ref: female)	–0.03	0.37	0.95	–1.37	0.55	0.01*
Age group 1 < 35 years (Ref: age group 3 > 50 years)	0.61	0.52	0.24	0.38	0.67	0.58
Age group 2 ≥ 35 and < 50 years (ref: age group 3 > 50 years)	0.59	0.46	0.20	0.87	0.60	0.15
Health status: very good (Ref: satisfactory)	0.47	0.88	0.59	–6.05	33.29	0.86
Health status: good (Ref: satisfactory)	–0.07	0.69	0.92	1.28	0.78	0.10
Health status: less good (Ref: satisfactory)	0.54	0.44	0.22	0.70	0.58	0.23
Health status: bad (Ref: satisfactory)	0.73	0.56	0.20	0.45	0.72	0.54
Having children (Ref: None)	0.04	0.45	0.93	–0.30	0.58	0.61
Household income: prefer not to say (Ref: 1500 up to 3000€)	–0.32	0.58	0.58	–1.01	0.82	0.22
Household income: < 500€ up to < 1500€ (Ref: 1500 up to 3000€)	–0.57	0.41	0.16	–0.53	0.52	0.30
Household income: 3000 to 5000€ and above (Ref: 1500 up to 3000€)	1.23	0.54	0.02*	1.23	0.64	0.05
Wishes[a] for having family provide informal care 1 (Ref: 3)	0.38	0.74	0.61	0.04	0.96	0.97
Wishes[a] for having family provide informal care 2 (Ref: 3)	0.32	0.75	0.67	1.45	0.80	0.07
Wishes[a] for having family provide informal care 4 (Ref: 3)	–0.45	0.48	0.35	–0.27	0.56	0.63
Wishes[a] for having family provide informal care 5 (Ref: 3)	–1.25	0.44	0.00*	–1.99	0.66	0.00*
Care experience (Ref: none)	–0.32	0.36	0.38	–0.93	0.46	0.04*

*$p<0.05$

[a]Wishes were ranked on a 5-point Likert scale, 1 not important and 5 very important

Discussion

This study investigated the willingness to provide informal care to older adults among 280 participants of the German general population by means of a DCE. With the help of qualitative interviews as well as a systematic literature review, five distinct aspects (attributes) were defined that influence a person's willingness to provide informal care. All of the included attributes were found to be statistically significant and thus relevant to the respondents when choosing between two hypothetical care situations. Almost all LTC systems around the world rely heavily on the support of informal caregivers and thus indirectly on the continuing willingness of people to provide informal care to their older or sicker relatives in need [4, 38]. Thus, the availability of informal caregivers is predominately determined by people's willingness to provide care and the support in place to enable informal caregiving [4]. Against the background of changing family structures, growing geographical distances between family members or the increasing employment rates of women, experts expect the rate of informal care to decrease in the future [39]. However, as many Germans still wish to 'age in place' and home-based care is considerably less costly for the state and the social security system, informal care remains an important pillar and research topic of interest. As the funding of the German LTC system is based on mandatory contributions, we chose to survey a sample of the general population. This study perspective as well as methodology used is an important distinction to other studies in the field that have predominately investigated the value of informal care by means of the contingent valuation method and surveying informal caregivers [18, 19, 21, 40].

When looking at the results of the CLM, the attribute care time constituted the most important attribute for the entire study population. As expected, needing to provide more hours of informal care per day was valued negatively. For the availability of informal caregivers in a country, a key determinant is the willingness of individuals to provide the number of care hours required for the care-dependent person [4]. Even though the needed care time per day or the expected duration of caregiving is difficult to plan ahead [6], it is important to know what people can imagine in terms of providing informal care. Studies show that with increasing care dependency, the necessary care time per day is often higher than our maximum level of 8 h care time per day [41, 42]. Nevertheless, the chosen level of 8 h was specifically intended to represent an equivalent to a full working day in Germany to additionally survey a willingness to reduce working hours if necessary. Other studies have also found that an increase in care hours per day often results in the reduction or temporary pause of working hours [8, 10].

One major challenge that is often described is the necessary reconciliation of informal care with other personal responsibilities, such as needing to work to ensure financial stability or having younger children at home to take care of. The heavy burden informal caregivers shoulder as a result of conflicting responsibilities often in turn lead to high physical and mental strain [7, 10]. One economic incentive for informal care provision that is discussed in politics is a monetary compensation paid to informal caregivers to increase peoples' willingness to care [43]. In Germany, the idea of such a monetary compensation would be paid in addition to the existing insurance benefits available to the care-dependent person, similar to other legal entitlements such as parental leave. Such a monetary compensation might ensure financial stability for the informal caregiver for a period of time by enabling a reduction of working hours [43]. As we included such a financial compensation as one attribute in our DCE, we were able to calculate WTA values for the different attribute levels. The highest WTA value of €14.54 per hour was found when being willing to provide 8 h of care in reference to 2 h of care per day, followed by €9.41 per hour when having to provide care for an estimated period of 5 years instead of six months. The current minimum wage in Germany is €9.82, which is considerably lower than the accepted value of €14.54 per hour of informal caregiving [44]. A similar approach was taken in the DCE by Mentzakis et al. (2011), however, to estimate monetary values for specific informal care tasks such as personal care or household tasks [22]. While several studies have found significant differences between WTA and WTP values [21, 45], a Dutch study by van den Berg et al. (2005) found only minor differences between WTP and WTA when it comes to informal care valuations [46].

Preference heterogeneity was additionally investigated in this study with a three-class LCM. Especially when it comes to the above-mentioned monetary compensation, a higher financial compensation had in fact the highest positive impact on the willingness to provide care of respondents in class 3 ($n = 102$). This could in part be explained by class 3 having a significantly lower household income at their disposal in reference to class 1. Class 1 ($n = 112$) placed the greatest negative weight by far on increasing care hours per day. For class 2 ($n = 66$), instead of care hours, an increase in the expected duration of caregiving had the greatest negative value and the greatest positive impact was found for daily formal care services. Monetary compensation had no significant impact on respondent's willingness to provide care in class 2. Class 2 had a significantly higher proportion of women and respondents without care experiences compared to class 3. Moreover, wishes in terms of people's willingness to receive informal care in the future had a significant impact in both classes 1 and 2 in reference to class 3. Both classes had a significantly lower proportion of study participants

that found it very important for their relatives to take care of them in the event of a care dependency. Thus, respondents of class 3 seemed to be very willing to provide informal care and in turn would wish for the same willingness by their relatives. While not statistically significant in our study, others have found determining factors for peoples' willingness to make use of informal care to include having children and living together with a partner [47].

To the best of our knowledge, our study is the first to investigate the willingness to provide informal care of the German general population by means of a DCE. While, in total, studies on LTC preferences in the field of older adult care have seen an increase over the past years, a direct comparison of our results to other studies in the field of informal care is challenging. However, as we included the attribute formal care services, one particular study of interest is the DCE conducted by Lehnert et al. (2018) in Germany. In this DCE, the authors also surveyed a sample of the general population to investigate preferences for home- and community-based formal care services. Two hypothetical care packages were distinguished in reference to five attributes: care time per day, service level, quality of care, number of caregivers per month, and a co-payment per month [23]. The results of the CLM can provide some indications towards the possible preferences or design of the attribute formal care services that was integrated in our DCE. Results of the study by Lehnert et al. (2018) show that very high quality of care and smaller groups of formal caregivers (less rotation) were preferred. The calculated WTP for one extra hour of formal care was €8.98 for the surveyed sample [23].

Limitations

This study has several limitations that need to be addressed. The sample was only recruited in one federal state of Germany (Lower Saxony), which means that transferability of study findings is limited. In addition, the response rate of 8.1% is considerably lower compared to other studies in the field of informal care (20%, [22]) or home-based care (23.4%, [23]). Unfortunately, a relatively high proportion of questionnaires also had to be excluded due to missing values (44 out of 324). This might be due to the complexity of the chosen method DCE combined with the research topic and postal survey. Due to the limited sample size, it was not appropriate to derive concrete policy suggestions or recommendations. For this reason, future studies should attempt to include a considerably larger and optimally German-wide sample to increase representativeness. Additionally, no reminder was sent in our study, as we believed that this topic of interest either sparked interest in participants or not. As previous qualitative work has shown that willingness to provide informal care is difficult for some to actively deal with until such a situation arises in the family, we believed that a reminder would not significantly increase participation [6]. Moreover, a considerably higher proportion of women participated in our study, which might also be explained by the research topic. We had similar challenges in our qualitative work in the field [6]. A sample selection bias is therefore possible and means interpretation of study results need to be done cautiously.

In the design of the DCE, we were unfortunately not able to integrate changes in the type and severity of the care dependency such as cognitive compared to physical impairments. As we expect this to have an impact on people's willingness to provide care, this should be integrated in future studies. It needs to be noted that willingness to provide care is additionally influenced by many other factors, such the relationship to the person in need of care, cultural and normative beliefs, as well as surrounding circumstances such as the geographical distance between family members or the available housing space [6]. The interpretation of these influencing factors were consciously left open to each study participant in the DCE as only the five attributes and the context of the care situation were provided. Moreover, the availability, quality, and affordability of near-by formal alternatives such as nursing homes might also impact willingness to provide informal care. This, however, is regionally very different in Germany and difficult to integrate in a DCE without substantially increasing the complexity of the choice sets. The use of a forced-choice design forced respondents to always choose between the two alternatives, even if in reality people might opt out and choose not to provide informal care.

Since our DCE data were only collected at one point in time, no temporal changes in people's willingness to care could be measured. As qualitative studies have shown that willingness to care is usually influenced by a number of complex contextual factors and can change over time with, for instance, altering personal responsibilities or changes in people's health status. Future studies should further investigate changes in people's willingness compared to the actual provision of informal care over time. Nevertheless, as some studies suggest that informal care will likely continue to decrease in the future, while the need for this type of care remains high, it remains important to investigate people's perceptions and general willingness to provide care. More specifically, it is vital to investigate which factors have a considerable impact on people's willingness to provide care, such as the included monetary compensation. Unfortunately, several independent variables had too little variation in our sample, which increased correlations between variables and made it impossible to estimate an effect of these variables on the class segmentation of the LCM. A bigger sample might enable the inclusion of further independent variables, such as the employment status in future studies.

Conclusion

The present study is the first that investigated people's willingness to provide informal care by means of a DCE. Willingness to provide care was decomposed into five distinct aspects (attributes). With the help of regression models, the relative importance and trade-offs between attributes could be inferred. Under the premise that informal care remains a vital pillar of the German LTC system, results can provide insights into structural aspects that need to be improved to ensure that people are willing to provide informal care without too much mental and physical strain, as this in turn often leads to higher health costs and work absenteeism. The results of our LCM showed that compared to preferences of our entire sample, preferences could be segmented into three distinct groups that placed a different focus on attributes. Care time per day and expected duration of caregiving were valued negatively, however, in the three groups to a significantly different extend. Class 1 placed by far the greatest negative weight on an increase in the care time by day. Class 2 had a lower proportion of people with caregiving experiences and placed the highest value on reducing the expected time period of caregiving as well as having daily formal care services for support. While a monetary compensation is discussed to increase the willingness and availability of informal care in a country, our results show that this statement could not be generalized to our entire sample. More specifically, a monetary compensation might therefore only reach and motivate a sample of the population (here class 3), in particular as our results show people with a lower household income at their disposal.

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Declarations

Conflict of interest The authors declare that there is no conflict of interest.

Ethical approval The study has been approved by the Committee for Clinical Ethics of the Medical School in Hannover, Germany (Reference number 09.05.17/La). The respondents provided their implicit consent by sending the completed questionnaire back to the contact person (lead author).

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Supplementary material

Table 1: Conditional logit model (*main effects + all two-way interaction effects*)

Attribute/Level	**Coefficient**	**OR**	**95% CI**	**SE**	***p*-value**
Duration (*Ref: 6 months*)					
2 years	1.44	4.23	(0.75; 2.13)	0.35	0.00*
5 years	–0.46	0.63	(–0.92; –0.01)	0.23	0.04*
Care time (*Ref: 2 hours/day*)					
5 hours/day	–1.12	0.33	(–1.64; –0.59)	0.27	0.00*
8 hours/day	–2.02	0.13	(–2.63; –1.41)	0.31	0.00*
Formal care services (*Ref: None*)					
3–4 times/week	1.43	4.19	(0.93; 1.94)	0.26	0.00*
Daily	–0.48	0.62	(–1.06; 0.11)	0.30	0.11
Respite (*Ref: None*)					
3 weeks/year	0.06	1.06	(–0.47; 0.59)	0.27	0.83
6 weeks/year	0.05	1.05	(–0.55; 0.65)	0.31	0.88
Monetary compensation (€/hour)	1.05	2.87	(0.77; 1.33)	0.14	0.00*
Interaction effects					
2 years x 5 hours/day	–0.39	0.68	(–0.91; 0.13)	0.27	0.14
2 years x 8 hours/day	–1.41	0.24	(–2.03; –0.78)	0.32	0.00*
2 years x 3–4 times/week	–1.00	0.37	(–1.54; –0.45)	0.28	0.00*
2 years x Daily	–0.45	0.63	(–1.05; 0.14)	0.30	0.14
2 years x 3 weeks/year	–1.09	0.34	(–1.79; –0.38)	0.36	0.00*
2 years x 6 weeks/year	–0.87	0.42	(–1.47; –0.28)	0.30	0.00*
2 years x Monetary compensation	–0.49	0.61	(–0.75; –0.22)	0.13	0.00*
5 years x 5 hours/day	–0.53	0.59	(–1.02; –0.04)	0.25	0.04*
5 years x 8 hours/day	–1.01	0.36	(–1.55; –0.48)	0.27	0.00*
5 years x 3–4 times/week	–0.71	0.49	(–1.27; –0.15)	0.29	0.01*
5 years x Daily	0.55	1.73	(0.06; 1.04)	0.25	0.03*
5 years x 3 weeks/year	–0.20	0.82	(–0.74; 0.33)	0.27	0.45
5 years x 6 weeks/year	0.20	1.23	(–0.36; 0.77)	0.29	0.48
5 years x Monetary compensation	–0.39	0.67	(–0.62; –0.17)	0.12	0.00*
5 hours/day x 3–4 times/week	0.62	1.87	(0.18; 1.07)	0.23	0.01*
5 hours/day x Daily	0.75	2.11	(0.14; 1.36)	0.31	0.02*
5 hours/day x 3 weeks/year	0.28	1.32	(–0.25; 0.80)	0.27	0.30
5 hours/day x 6 weeks/year	0.16	1.18	(–0.36; 0.69)	0.27	0.54
5 hours/day x Monetary compensation	–0.23	0.79	(–0.49; 0.02)	0.13	0.08
8 hours/day x 3–4 times/week	0.78	2.19	(0.14; 1.43)	0.33	0.02*
8 hours/day x Daily	–0.74	0.48	(–1.46; –0.02)	0.37	0.04*
8 hours/day x 3 weeks/year	0.99	2.70	(0.42; 1.57)	0.29	0.00*
8 hours/day x 6 weeks/year	1.19	3.30	(0.60; 1.79)	0.30	0.00*
8 hours/day x Monetary compensation	–0.26	0.77	(–0.56; 0.05)	0.16	0.10
3–4 times/week x 3 weeks/year	0.21	1.24	(–0.36; 0.78)	0.29	0.46
3–4 times/week x 6 weeks/year	–0.32	0.73	(–0.82; 0.18)	0.25	0.20
3–4 times/week x Monetary compensation	–0.03	0.97	(–0.29; 0.22)	0.13	0.80
Daily x 3 weeks/year	2.41	11.18	(1.82; 3.01)	0.30	0.00*
Daily x 6 weeks/year	1.55	4.70	(0.99; 2.11)	0.29	0.00*
Daily x Monetary compensation	0.21	1.23	(–0.06; 0.48)	0.14	0.13
3 weeks/year x Monetary compensation	–0.07	0.93	(–0.31; 0.16)	0.12	0.55
6 weeks/year x Monetary compensation	–0.16	0.85	(–0.42; 0.11)	0.13	0.24
Log likelihood	–2296.7				
Pseudo R^2	0.22467				
AIC	4675.4				
BIC	4914.4				
No. of observations	5030				
No. of coefficients	41				

**significant at p<0.05, Monetary compensation is standardized*

Table 2: Socio-demographic structure of the classes within the LCM

	Class 1 (n = 122)	**Class 2 (n = 66)**	**Class 3 (n = 102)**
Sex			
Male	38 (33.93)	9 (13.64)	34 (33.33)
Female	74 (66.07)	57 (86.36)	68 (66.67)
Age group			
<35 years	37 (33.06)	16 (24.24)	23 (22.55)
≥35 & <50 years	29 (25.89)	22 (33.33)	18 (17.65)
>50 years	46 (41.07)	28 (42.42)	61 (59.80)
Health status			
Very good	26 (23.21)	10 (15.15)	13 (12.75)
Good	55 (49.11)	34 (51.51)	43 (42.16)
Satisfactory	23 (20.54)	12 (18.18)	30 (29.41)
Less good	5 (4.46)	10 (15.15)	12 (11.76)
Bad	3 (2.68)	0 (0.00)	4 (3.92)
Having children			
Yes	73 65.18)	44 (66.67)	72 (70.59)
No	39 (34.82)	22 (33.33)	30 (29.41)
Household income			
Prefer not to say	10 (8.93)	4 (6.06)	12 (11.76)
<500€ – 1500€	27 (24.11)	20 (30.30)	45 (44.12)
1500€ – 3000€	45 (40.18)	24 (36.36)	38 (37.25)
3000€ – 5000€ and more	30 (26.79)	18 (27.27)	7 (6.86)
Wishes			
1 (not important)	9 (8.04)	3 (4.55)	5 (4.90)
2	8 (7.14)	12 (18.18)	4 (3.92)
3	37 (33.04)	22 (33.33)	19 (18.63)
4	29 (25.89)	19 (28.79)	20 (19.61)
5 (very important)	29 (25.89)	10 (15.15)	54 (52.94)
Care experiences			
Yes	71 (63.39)	31 (46.97)	63 (61.76)
No	41 (36.61)	35 (53.03)	39 (38.24)

Note: The absolute and relative numbers per class are shown.

Modul 2

PICCA study: panitumumab in combination with cisplatin/gemcitabine chemotherapy in KRAS wild-type patients with biliary cancer - a randomised biomarker-driven clinical phase II AIO study

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Original Research

PICCA study: panitumumab in combination with cisplatin/gemcitabine chemotherapy in KRAS wild-type patients with biliary cancer—a randomised biomarker-driven clinical phase II AIO study

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KEYWORDS
Bilary cancer;
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Panitumumab;
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EGFR

Abstract ***Background:*** Combination chemotherapy has shown benefit in the treatment of biliary cancer and further improvements might be achieved by the addition of a biological agent. We report here the effect of chemotherapy with the monoclonal EGFR antibody panitumumab as therapy for KRAS wild-type biliary cancer.
Patients and methods: Patients with advanced biliary tract cancer were randomised (2:1) to receive cisplatin 25 mg/m^2 and gemcitabine 1000 mg/m^2 on day 1 and day 8/q3w with (arm A) or without panitumumab (arm B; 9 mg/kg BW, i.v q3w). The primary end-point was the evaluation of progression-free survival (PFS) at 6 months. Secondary end-points included objective response rate (ORR), overall survival (OS), and toxicity. In addition, a post hoc assessment of genetic alterations was performed. Finally, we performed a meta-analysis of trials with chemotherapy with and without EGFR antibodies.
Results: Sixty-two patients were randomised in arm A and 28 patients in arm B. Patients received 7 treatment cycles in median (1–35) with a median treatment duration of 4.7 months (141 days, 8–765). PFS rate at 6 months was 54% in patients treated with cisplatin/gemcitabine and panitumumab but was 73% in patients treated with cisplatin/gemcitabine without antibody, respectively. Secondary end-points were an ORR of 45% in treatment arm A compared with 39% receiving treatment B and a median OS of 12.8 months (arm A) and of 20.1 months (arm B), respectively. In contrast to the p53-status, genetic alterations in IDH1/2 were linked to a high response after chemotherapy and prolonged survival. In accordance with our results, the meta-analysis of 12 trials did not reveal a survival advantage for patients treated with EGFR antibodies compared with chemotherapy alone.
Conclusions: Panitumumab in combination with chemotherapy does not improve ORR, PFS and OS in patients with KRAS wild-type, advanced biliary cancer. Genetic profiling should be included in CCA trials to identify and validate predictive and prognostic biomarkers.
Clinical Trials Number: The trial was registered with NCT01320254.

1. Introduction

Biliary tract cancer (BTC) is an epithelial cancer originating from the bile ducts with features of cholangiocyte differentiation. It is the second most common primary hepatic malignancy, and epidemiologic studies shows a rising incidence in Western countries [1,2]. Hepatobiliary malignancies account for 13% of the 7.6 million annual cancer-related deaths worldwide and CCA accounts for approximately 20% of the deaths from hepatobiliary malignancies. Most patients are diagnosed in an advanced-stage cancer making them ineligible for potentially curative resection and even after successful resection recurrence rate is high [3,4].

Currently, platinum- and gemcitabine-based chemotherapy is the standard first-line treatment based on results of one phase III and one phase II study in which median overall survival (OS) was longer in the combination arm with gemcitabine and cisplatin compared with the gemcitabine monotherapy arm ($p = 0.002$) [5].

The growing understanding of the molecular pathogenesis of CCA opens new therapeutic options for targeted therapies. In particular, EGFR signalling appears to be important for tumour growth of CCA with EGFR being overexpressed in 67–100% of biliary cancers. KRAS is a downstream molecule in the EGFR pathway. Data on metastatic colorectal cancer have shown that the monoclonal EGFR antibodies are only active in patients with tumour-absent KRAS and NRAS mutations, which comprise about 50% of all colorectal carcinomas [6]. Dysregulation of KRAS is commonly observed in malignancies, and mutations of KRAS have been described in up to 50% of CCAs, which was also confirmed in the most recent data from the TCGA consortium [7]. So far, it is not clear whether the RAS status does predict response in CCAs similarly to colorectal cancer.

The primary objective of the present study was to determine the efficacy of panitumumab plus gemcitabine/cisplatin (CisGem) combination chemotherapy in

KRAS wild-type biliary tract cancer patients, including patients with gallbladder cancer, without systemic pretreatment, compared with the historical data for standard CisGem chemotherapy, which are verified by a randomised control group without the EGFR antibody.

2. Patients and methods

2.1. Eligibility criteria

Eligible patients were at least 18 years of age with a histologically documented CCA or gallbladder carcinoma, a wild-type KRAS-status as assessed by standardised Sanger sequencing and an ECOG performance status of 0–2. No prior systemic therapy was allowed, and life expectancy had to be at least 12 weeks.

2.2. Study design and treatment

In this open-label phase II clinical trial, patients were randomised at a 2:1 ratio to either panitumumab 9 mg/kg on days 1 and 8 of a 21-day cycle and cisplatin 25 mg/m^2 and gemcitabine 1000 mg/m^2 on days 1 and 8 of a 21-day cycle (arm A) or cisplatin 25 mg/m^2 and gemcitabine 1000 mg/m^2 on days 1 and 8 of a 21-day cycle (arm B). Patients were stratified according to gallbladder versus cholangiocarcinoma, leucocytes $<8000/\mu L$ versus $\geq 8000/\mu L$ and alkaline phosphatase <300 U/L versus $\geq$ 300 U/L. All doses were based on the actual body weight and were administered intravenously.

The protocol was approved by the regional ethics committee and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent at the time of enrolment. The trial was registered with the NCT01320254 identifier.

2.3. Study evaluations

All eligible patients with CCA or gall bladder carcinoma for the clinical trial had a screening examination including medical history, physical examination, recording of ECOG performance status, computed tomography scan of chest and abdomen, blood chemistries, blood counts and *KRAS* mutational status.

During treatment, blood counts were repeated before every treatment, blood chemistries and evaluation of toxicity were repeated at every 3 weeks, and physical examination, evaluation of performance status and tumour evaluation were repeated every second cycle. If treatment was stopped before progression, the patient was followed clinically and radiologically every 3 months until progression. Response was assessed by RECIST. After progression, only date and cause of deaths were recorded. Treatment after exclusion from the study was according to the department's guidelines.

For post hoc broad genetic profiling, massive parallel multigene sequencing was done by using a custom designed biliary cancer multigene panel covering hotspot regions of 40 genes on an IonTorrent Proton system. Mutations as well as amplifications and deletions (19 genes) were identified by panel-tailored bioinformatic algorithms.

2.4. Statistics

The primary end-point was the progression-free survival (PFS) rate at 6 months, based on the ITT population (the rate is defined as the number of patients recorded to be free of progression at this time point, divided by the number of patients randomised to the respective arm). Within the explorative phase II framework, a time-to-event rate is often used as primary end-point for the detection of a signal of promising efficacy. We chose this option for two reasons: 1. to allow for the application of a conventional FLEMING-type design for sample size calculation, 2. as this rather 'early' end-point allows for an analysis after a reasonably short period of time.

Secondary end-points were tumour response within the first 48 weeks of treatment, median PFS, OS and toxicity. In addition, correlation of tumour response and survival with genetic alterations in cholangiocarcinomas and gallbladder cancer was assessed.

The experimental therapy arm would be rated as insufficiently active, if the true PFS rate is 60% or lower, as this corresponds to the efficacy of two-drug chemotherapy combinations alone. It would be considered to be a highly promising candidate for further development (e.g. in a phase III trial), if the true PFS rate amounted to 75% or more. The risk of type 1 and 2 error was set at 0.05 and 0.2, respectively, corresponding to a power of 80%, corresponding to a power of 80%, resulting in a sample size requirement of 61 patients in the experimental arm, according to a design by Fleming. Arm B served as a randomised reference group to verify the historical assumptions, and to control for selection bias.

Non-parametric methods (including Wilcoxon and Mann–Whitney test or Fisher's exact test) were used to compare patient characteristics and toxicity.

Time-to-event end-points (PFS and OS) were estimated by the Kaplan–Meier method and were calculated from date of randomisation. Response was calculated for patients with measurable disease at baseline. The best response was recorded and clinical progression or death before the first evaluation was considered progressive disease.

Eligible patients were analysed for PFS and OS (ITT population). All patients who received at least one dose of study medication were evaluated for safety. Toxicity was evaluated using Common Terminology Criteria for Adverse Events version 3.0.

The predictive value of the genetic alterations was analysed using Kaplan–Meyer plot and log-rank test (two-sided).

2.5. Meta-analysis

The meta-analysis was conducted according to PRISMA guidelines [8]. The data analysis was performed based on the methodology proposed by Combescure *et al.* [9]. First, for each study, conditional survival probabilities were calculated from the reconstructed individual data at fixed time periods of one month. The conditional probabilities were then pooled by applying the extension of DerSimonian and Laird's univariate methodology for multiple outcomes [9,10]. Pooled survival probabilities were obtained by the product of the pooled conditional survival probabilities. Finally, based on the pooled data, a summary survival curve was constructed and summary statistics (median survival, hazard ratios) were calculated. Confidence intervals (95%) were obtained by bootstrap procedures. All calculations were performed in R software, version 3.1.2 (http://www.r-project.org/). Additional information on the meta-analysis can be found in the suppl. methods.

3. Results

3.1. Baseline

From July 2011 until December 2015, 93 patients were included in 17 centres in Germany. Out of those 3 patients were not eligible either due to inability to determine *KRAS* mutational status, due to missing informed consent or due to previous treatment with gemcitabine (1 patient each). Of the remaining 90 patients, who were defined as the IIT population, 85 were evaluable for analysis of the primary end-point. Median age of the IIT population was 61.5 years, range 18–82 years with 56% were male patients. Baseline characteristics of the ITT are shown in Table 1.

Table 1
Patient characteristics at baseline.

Variable	Arm A (n = 62)	Arm B (n = 28)	Total (n = 90)
Age (median [range], years)	62 (18–82)	59.5 (22–76)	61.5 (18–82)
Sex, n			
Female	26	14	40
Male	36	14	50
PS, n			
0	39	17	56
1	19	11	30
2	2	0	2
Time from primary diagnosis to inclusion (median [range], mo.)	1.5 (0.5–105.8)	1.5 (0.5–101.7)	1.5 (0.5–105.8)
Localisation, n			
Gall bladder	11	3	14
Distal	7	1	8
Perihilar	2	2	4
Intrahepatic	41	20	61
others	6	6	12
Surgery, n			
Yes	28	13	41
No	34	15	49
Tumour burden			
M0	13	5	18
M1	42	17	59
Mx	7	6	13
M localisation			
Liver	53	22	75
Lung	11	5	16
Bone	3	2	5
Lymphnodes	37	19	56
Co-morbidities, n			
Yes	53	25	78
No	9	3	12

3.2. Treatment

The patients in arm A (cisplatin/gemcitabine and panitumumab) received 8 cycles of treatment in median (range 1–35), and 6 cycles (range 1–16) in arm B (cisplatin/gemcitabine without panitumumab) and 7 cycles (range 1–35) in total. Median duration of therapy was 156 days, range 8–765 in arm A, 130.5 days, range 8–329 in arm B and 141 days, range 8–765 in total. Patients received a median panitumumab dose of 9 mg/kg, range 0–9.5 and a cumulative dose of 63 mg/kg, range 0–248.5.

Reasons for stopping treatment (in total) were progression (n = 49), death (n = 7), toxicity (n = 22), patient's wish (n = 7) and other reasons (n = 10). Dose modification in the chemotherapy arm (B) was seen in 83% of patients and in the panitumumab arm (A) in 73%. Reduction of panitumumab dosages took place in 39%.

3.3. Efficacy

In arm A (cisplatin/gemcitabine + panitumumab), 32 of 59 patients (54%; 95% confidence interval (CI):41%–67%) of 59 patients were progression-free after 6 months with a mPFS of 6.6 months. In arm B (cisplatin/gemcitabine), PFS rate at 6 months was documented for 19 of 26 patients (73%; 95% CI: 52%–88%) with a mPFS of 8.3 months, as shown in Fig. 1. The sensitivity analysis showed no relevant differences to the ITT analysis. There were a total of 39 responders (43%) out of 90 patients; 45% responders were recorded in treatment arm A, whereas 39% responded to the treatment provided in arm B. Overall survival is presented in Fig. 2 using the Kaplan–Meier plots. Median OS was 12.8 months in patients treated with cisplatin/gemcitabine + panitumumab and 20.1 months in patients treated with cisplatin/gemcitabine (p = 0.18, two-sided).

3.4. Toxicity

Eighty-seven patients received at least one application of study therapy and were eligible for toxicity assessment.

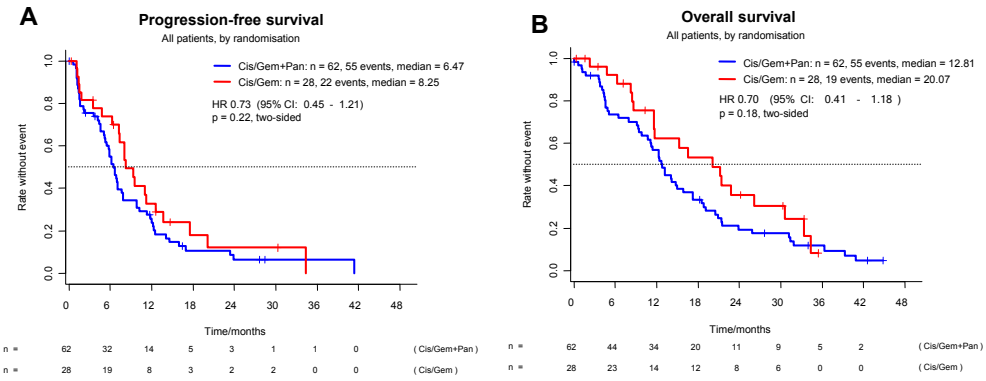

Fig. 1. A: Progression-free survival of all randomised patients. B: overall survival of all randomised patients.

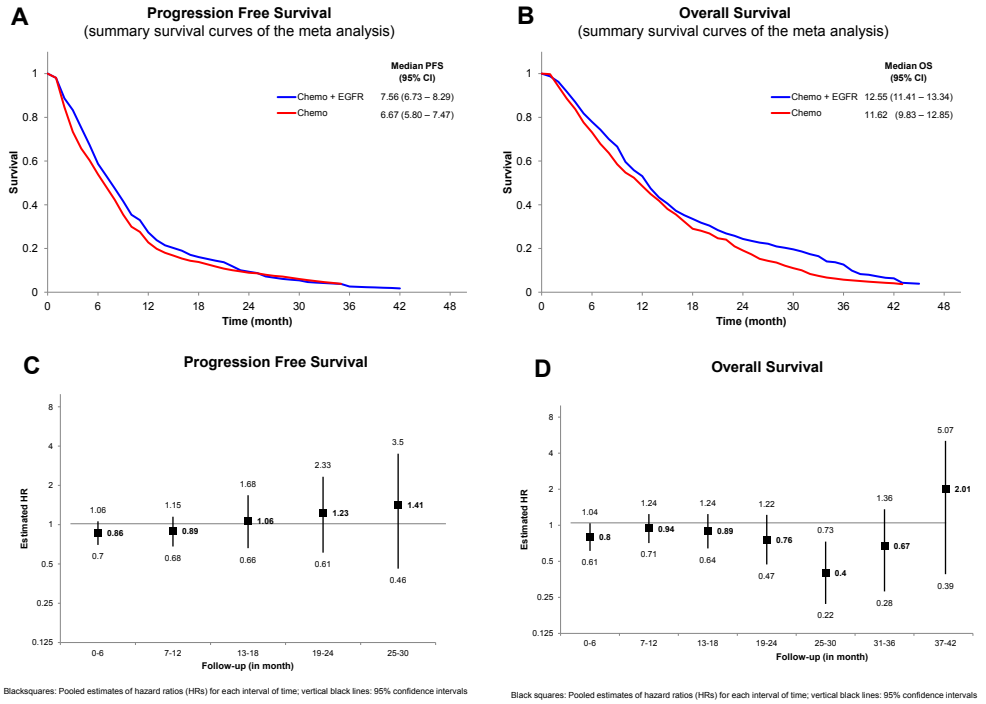

Fig. 2. A + B: Summary survival curves of the meta-analysis. A) Progression-free survival. B) Overall survival. C + D: Pooled estimates of hazard ratios (HRs) for each interval of time. C) Progression-free survival. D) Overall survival.

Table 2 presents frequent drug-related adverse events both in absolute numbers and percentages for grade 1–2 and grade ≥3 for both treatment arms. The safety profile of panitumumab was similar to previous trials: skin toxicities including rash, acne and dry skin and gastrointestinal toxicities including diarrhoea and mucositis were more frequent in the panitumumab arm than in the Gem/Cis arm. During therapy, 6 patients died due to tumour progression, and one due to a myocardial infarction. No deaths due to toxicity occurred.

Table 2
Frequent drug-related adverse events.

Adverse events	Gem/Cis + panitumumab (n = 59)		GemCis (n = 28)	
	Grade 1–2	Grade ≥3	Grade 1–2	Grade ≥3
Haematological toxicities				
Leucopenia	30 (51%)	13 (22%)	18 (65%)	8 (29%)
Neutropenia	16 (27%)	26 (44%)	11 (39%)	13 (47%)
Febrile neutropenia	1 (2%)	3 (5%)	0	0
Thrombopenia	24 (41%)	18 (21%)	8 (29%)	12 (43%)
Anaemia	41 (70%)	7 (12%)	19 (68%)	3 (11%)
Skin toxicities				
Dry Skin	37 (62%)	3 (5%)	0	0
Nail changes	17 (29%)	1 (2%)	0	0
Rash	27 (46%)	7 (12%)	5 (18%)	0
Acne	30 (51%)	10 (17%)	4 (14%)	0
Gastrointestinal toxicities				
Diarrhoea	18 (30%)	3 (5%)	2 (8%)	0
Mucositis	28 (47%)	0	7 (25%)	1 (4%)
Nausea	29 (49%)	2 (3%)	18 (64%)	1 (4%)
Other toxicities				
Fatigue	40 (68%)	4 (7%)	21 (75%)	0
Fever	16 (27%)	0	3 (11%)	0
Infection	18 (31%)	6 (10%)	18 (64%)	6 (21%)
Neuropathy	16 (27%)	0	8 (29%)	0
Dyspnoea	12 (20%)	1 (2%)	4 (15%)	0

3.5. Meta-analysis

Twelve studies were included in the analysis, resulting in the assessment of 5 study arms using combination chemotherapy (410 patients) and 11 study arms using chemotherapy + anti-EGFR antibody (514 patients). The PRISMA flow diagram of the systematic review is presented in suppl. figure 1. Four studies included only patients with KRAS WT tumours. Details of included studies are summarised in suppl. table 1. Estimated summary survival curves are illustrated in suppl. figure 2–5. Median PFS of combination chemotherapy and chemotherapy + anti-EGFR was 6.7 (95% CI: 5.80–7.47) and 7.6 (95% CI: 6.73–8.29), respectively (see Fig. 2A). Median OS of combination chemotherapy and chemotherapy + anti-EGFR was 11.6 (95% CI: 9.83–12.85) and 12.6 (95% CI: 11.41–13.34), respectively (see Fig. 2B). Pooled estimates of PFS and OS hazard ratios (see Fig. 2C+D) revealed a positive treatment effect when adding anti-EGFR antibodies to chemotherapy, which was however limited to the time interval 25–30 month after treatment start. A separate analysis of RCTs only (suppl. Fig. 6–11) resulted in lower median PFS and OS for both groups, chemotherapy and chemotherapy + anti-EGFR antibody, and no significant improvements in PFS or OS were detected.

Between-study heterogeneity was low in OS (combination chemotherapy: $H^2 = 1.02$, $I^2 = 0.03$; chemotherapy + anti-EGFR antibody: $H^2 = 1.07$, $I^2 = 0.06$) and low-moderate in PFS (combination chemotherapy: $H^2 = 1.46$, $I^2 = 0.32$; chemotherapy + anti-EGFR antibody: $H^2 = 1.35$, $I^2 = 0.26$).

3.6. Genetic profiling

To assess the correlation of tumour response and survival with genetic alterations in cholangiocarcinomas and gallbladder cancer (genetic profiling), 83 tumours were analysed by a panel sequencing for 40 genes (see suppl. Fig. 12). Out of these, 75 were randomised in the trial. Alterations of isocitrate dehydrogenase (IDH) 1/2 were detected in 13% of tumours, all of them were iCCA (11 patients), and TP53 mutations were present in 27% (22 patients) of all analysed tumours as shown in Fig. 3.

To assess the prognostic and predictive value of the most frequently observed genetic alterations, TP53 and IDH1/2, survival of the patients with WT and mutant tumours were analysed. As shown in Fig. 4A, there was no significant difference in mOS for patients with TP53 WT and mutant tumour with 12.7 and 12.8 months. Similarly, we did not observe any response difference in patient with mutations in nRAS, bRAF or PIK3CA downstream in the EGFR signalling cascade (7 'mutant' patients with mPFS 7.0 month (1.4–41.6) and mOS 12.3 (2.4–44.8 months).

In contrast, mOS in patients with IDH1/2 mutations, all patients with intrahepatic CCAs, was significantly and clinically meaningful longer compared with patients with all WT tumours (28.2 months [n = 9] versus 11.6 months [n = 66], p = 0.025; see Fig. 4B). A similar effect was also seen when only comparing IDH1/2 mutant and WT iCCAs (28.2 months [n = 9] versus 11.6 months [n = 46], p = 0.076; suppl. Fig. 13). In accordance with the prolonged mOS, all patients achieved a

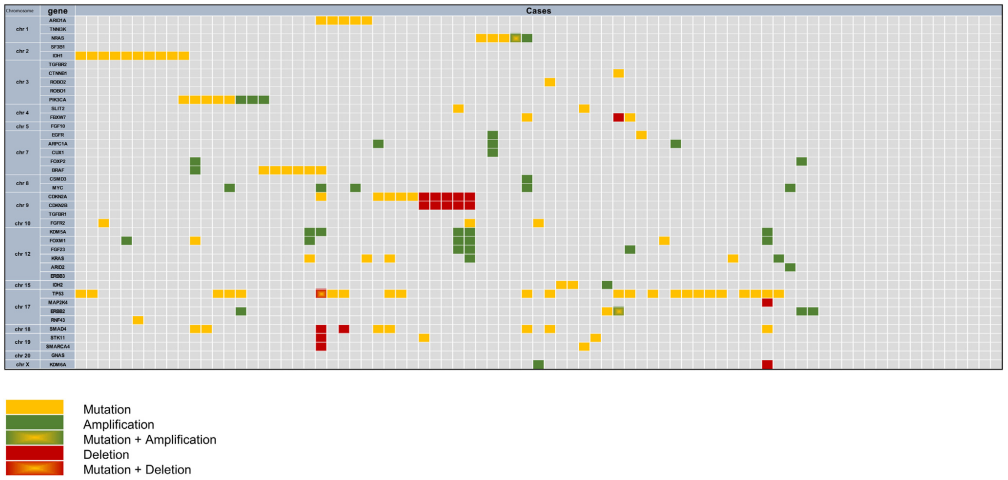

Fig. 3. Overview of identified genetic alterations in 40 genes.

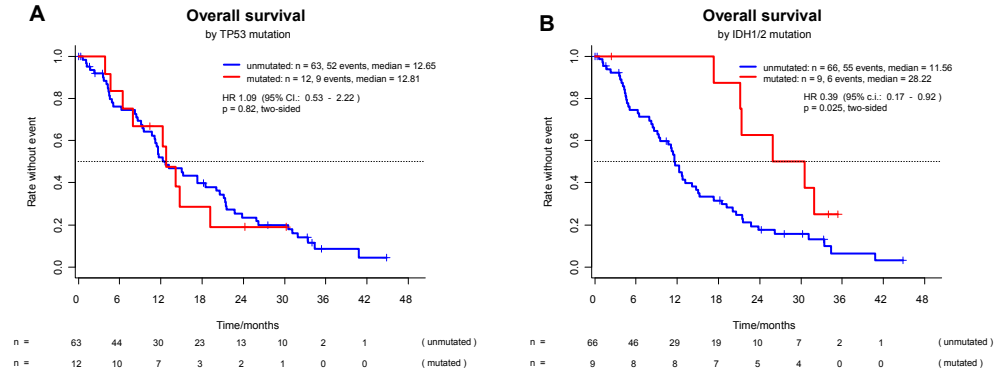

Fig. 4. A: Overall survival of patients with TP53 WT compared to TP53 mutant tumours. B: Overall survival of patients with IDH1/2 WT compared to IDH1/2 mutant tumours.

PR under platinum-based chemotherapy and mPFS was significantly longer in patients with mIDH1/2 (suppl. Fig. 14).

4. Discussion

The purpose of the present trial was to evaluate the efficacy of chemotherapy and panitumumab in patients with *KRAS wild-type* biliary cancers. In this trial, panitumumab in combination with chemotherapy does not improve the 6-month PFS rate, the median PFS, ORR and median OS in patients with *KRAS WT*, advanced BTC. Moreover, a persistently inferior survival was observed for the combination arm compared with the control arm. No imbalances in prognostic factors such tumour location, baseline lab values or tumour markers were evident to explain this observation. The toxicity profile was similar to previous trials with skin toxicities and gastrointestinal toxicities being more frequent in the panitumumab arm than in the Gem/Cis arm, but chemotherapy dose intensity was similar in both arms.

To discuss our data in the context of the already published literature, we performed a systematic meta-analysis. Overall, 5 randomised and 7 single-arm studies with EGFR-antibodies in combination with platinum-based chemotherapy in advanced CCA were identified. Out of these 11 studies, 4 were marker-driven trials with panitumumab in *KRAS* WT biliary cancer patients. In none of the comparative studies, mOS was significantly

improved compared with the control arm indicating that the addition of EGFR-antibodies to platinum-based chemotherapies in first-line treatment does not improve outcome in CCA patients. To detect any survival benefit in patients treated with EGFR antibodies, a meta-analysis of all published trials and the trial reported herewith was performed. A recently published meta-analysis identified three RCTs which investigated the efficacy of EGFR antibodies plus chemotherapy versus combined chemotherapy in the treatment of patients with advanced BTC [11]. Pooled data of the three studies and an RCT evaluating erlotinib + chemotherapy resulted in a significantly higher median PFS (1.49 month; 95% CI: 0.43–2.56 month) but no additional benefit in median OS (0.07 month; 95% CI: −1.77–1.91 month). In contrast to the study by Chen *et al.*, our analysis only focused on studies with EGFR antibodies and was not restricted to RCTs. The results of our meta-analysis did not reveal evidence for either a sustained clinical benefit or harm of combining anti-EGFR antibodies with chemotherapies in this tumour entity, neither in the analysis of all studies nor in the separate analysis of RCTs only.

Although intrahepatic, perihilar and extrahepatic CCAs share morphologic features and are usually all included in most clinical trials, recent studies have revealed a high intertumoural genetic heterogeneity among CCAs with potential implications for clinical management. In agreement with recent studies, we observed TP53 mutations in 27% and IDH 1/2 mutations in 13% of our patients. All IDH 1/2 mutations were detected in iCCA patients in agreement with previous findings. Mutations in TP53 were without prognostic and predictive value in our cohort. Interestingly, tumour control, mPFS and mOS of patients with IDH1/2 mutations were significantly longer compared with WT patients. It is known that mutation of the IDH1/2 results in an abnormal production of 2-hydroxyglutarate (2-HG) thereby inhibiting a KG-dependent dioxygenases involved in epigenetic regulation, extracellular matrix maturation, and cell signalling. A recent integrative genomic analysis revealed unique molecular and histopathological characteristics of IDH mutant iCCA with potential prognostic and predictive relevance [7]. In contrast to four retrospective studies with mainly early-stage disease and conflicting data on the prognostic role of IDH1/2 mutation [12], our patients were prospectively evaluated and all received a Gem/Cisplatin-based chemotherapy. The underlying reason for the potentially higher sensitivity of IDH1/2 mutant patients to platinum-based chemotherapy is unclear but might be related to the recently identified *BRCAness* phenotype due to a homologues recombination defect of IDH1/2 mutant cancers [13]. Our data support the concept to exploit the biological consequences of mutant IDH, in addition to block 2HG production by mIDH1/2 inhibitors. In addition, our data indicate that platinum-based chemotherapy may not be combined with IDH1 inhibitors, which may reverse the *BRACness* phenotype of these tumours. Our data however need to be confirmed in future prospective trials.

In conclusion, panitumumab in combination with chemotherapy does not improve ORR, PFS and OS in patients with KRAS WT, advanced biliary tract cancer. In accordance with our analysis, a meta-analysis of 12 trials with 514 patients treated with chemotherapy in combination with EGFR antibodies and 412 chemotherapy-treated patients did not reveal a sustained survival benefit for patients treated with EGFR antibodies compared with chemotherapy alone. Further investigations of chemotherapy in combination with anti-EGFR antibodies are not warranted. The genetic heterogeneity in CCA requires stringent translational research to improve outcome of patients with this devastating disease and genetic profiling should be included in future prospective trials. IDH1/2 mutations may represent an interesting biomarker for biliary tumours not only for new targeted therapies but also for conventional platinum-based chemotherapy.

Authors' contribution

Arndt Vogel and Stefan Kubicka contributed to literature search, study design, data collection, data analysis, data interpretation, writing.

Stefan Kasper contributed to data collection, data analysis and writing.

Marianne Sinn, Henning Schulze-Bergkamen, Markus Hermann Moehler, Kirsten Elisabeth Merx, Elisabeth Schnoy, Jens T. Siveke, Patrick Michl, Dirk Waldschmidt, Jan Kuhlmann, Michael Geissler, Christoph Kahl contributed to data collection and analysis.

Wilko Weichert, Nicole Pfarr, Volker Endris, Benjamin Goeppert contributed to data analysis, data interpretation, writing.

Torben Schmidt and Alexander Kuhlmann contributed to data analysis, data interpretation, writing.

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Conflict of interest statement

Stefan Kasper reports personal fees from Amgen, outside the submitted work.

Michael Bitzer reports personal fees from BMS, MSD, Bayer Health Care and Ipsen, outside the submitted work.

Dr. Vogel reports personal fees from Amgen, Merck, Roche, Bayer, Lilly and BMS, outside the submitted work.

Dr. Weichert reports personal fees from MSD, BMS, Novartis, Boehringer and Pfizer, grants and personal fees from Roche and AZ, grants from Bruker, outside the submitted work.

All other authors do not have any conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejca.2017.12.028.

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Modul 3

Social/economic costs and health-related quality of life in patients with juvenile idiopathic arthritis in Europe

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ORIGINAL PAPER

Social/economic costs and health-related quality of life in patients with juvenile idiopathic arthritis in Europe

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Abstract
Objective The aim of this study was to determine the economic burden from a societal perspective and the health-related quality of life (HRQOL) of patients with juvenile idiopathic arthritis (JIA) in Europe.
Methods We conducted a cross-sectional study of patients with JIA from Germany, Italy, Spain, France, the United Kingdom, Bulgaria, and Sweden. Data on demographic characteristics, healthcare resource utilization, informal care, labor productivity losses, and HRQOL were collected from the questionnaires completed by patients or their caregivers. HRQOL was measured with the EuroQol 5-domain (EQ-5D-5L) questionnaire.
Results A total of 162 patients (67 Germany, 34 Sweden, 33 Italy, 23 United Kingdom, 4 France, and 1 Bulgaria) completed the questionnaire. Excluding Bulgarian results, due to small sample size, country-specific annual health care costs ranged from €18,913 to €36,396 (reference year: 2012). Estimated direct healthcare costs ranged from €11,068 to €22,138; direct non-healthcare costs ranged from €7837 to €14,155 and labor productivity losses

Members of the BURQOL-RD Research Network listed in Supplementary Annex 1.

Electronic supplementary material The online version of this article (doi:10.1007/s10198-016-0786-1) contains supplementary material, which is available to authorized users.

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ranged from €0 to €8715. Costs are also shown to differ between children and adults. The mean EQ-5D index score for JIA patients was estimated at between 0.44 and 0.88, and the mean EQ-5D visual analogue scale score was estimated at between 62 and 79.

Conclusions JIA patients incur considerable societal costs and experience substantial deterioration in HRQOL in some countries. Compared with previous studies, our results show a remarkable increase in annual healthcare costs for JIA patients. Reasons for the increase are the inclusion of non-professional caregiver costs, a wider use of biologics, and longer hospital stays.

Keywords Rare diseases · Juvenile idiopathic arthritis · Costs · Costs of illness · Quality of life

JEL Classification I1

Introduction

Juvenile idiopathic arthritis (JIA) is a general term for a group of conditions characterized by chronic arthritis with no defined cause. The disease commonly occurs in children before the age of 16 and lasts for a minimum of 6 weeks. According to the results of the International League of Associations for Rheumatology (ILAR) Meeting in 2001, JIA combines the following seven subtypes: systemic arthritis, oligoarthritis, rheumatoid-factor-negative polyarthritis, rheumatoid-factor-positive polyarthritis, psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis. These subtypes represent heterogeneous and autonomous diseases, apart from the undifferentiated arthritis, which defines diseases that cannot be classified or are related to more than one of the above subtypes [1]. The prevalence in Europe ranges from 4.2 to 20.5 per 100,000, depending on the specific subtype [2]. Country-specific values are not available.

The progression of JIA varies across the subtypes in terms of the number and type of inflamed joints, type of complication (fever or rash), time of occurrence, and the duration. Consequently, children with JIA are under threat of suffering from long-term complaints like joint destruction. Treatment of JIA is subject to the subtype. In general, it combines drug treatment, physiotherapy, occupational therapy, and, if required, psychological therapy [1]. The drug therapy covers a broad spectrum of medicines, e.g., non-steroidal anti-inflammatory agents, intra-articular corticosteroid injections, disease-modifying anti-rheumatic drugs, anti-interleukin therapy, and biologics. The choice of medication depends on the subtype of JIA [3].

The aim of this study was to estimate JIA-related social/economic costs in Europe. We provide analysis of the related costs, including direct healthcare costs, direct non-healthcare costs (formal and informal care) and loss of labor productivity. We quantify health-related quality of life (HRQOL) for patients with JIA and JIA-related non-professional caregivers. We provide our analysis on samples obtained during 2012 from eight EU countries.

Methodology

Research design and subjects This was a cross-sectional study of people diagnosed with JIA who received outpatient care and were living in the community. All patients and caregivers were informed about the study objectives and data confidentiality and were asked to state their understanding of the study conditions and agreement to participate. Cases were recruited from the specific JIA associations and registries. The survey was completely anonymous, as the patients were contacted by their patient organization and their responses were sent directly to the researchers without any identification data (name, identification, address, e-mail).

Information and variables of interest The fieldwork was carried out between September 2011 and April 2013. Questionnaires were administered by e-mail and postal survey through patient organizations. The information sources used in the study were the self-completed questionnaire filled out by patients and their caregivers. Demographic and clinical data were collected from patients diagnosed previously with JIA and their caregivers.

Most studies of cost-of-illness and HRQOL use information gathered at a specific point in time. The questionnaire we used was detailed enough to reduce either exaggeration or underestimation. To estimate resource utilization, the questionnaire solicited information covering the 6-month period prior to the study (12 months for hospitalizations). Data for the preceding 6 months were extrapolated to the entire year. We considered 6 months to be an appropriate recall period. Patients and caregivers were asked about reductions in working time (temporary and permanent sick leave or early retirement), and these data were used to estimate losses of labor productivity. Also, when care was provided by non-professional caregivers, they were asked about the informal care time. Information about HRQOL was collected from JIA patients through the generic EuroQol 5-domain (EQ-5D) questionnaire [4].

Costing methodology We used the prevalence approach to estimate costs from a societal perspective. Disease prevalence takes into account all existing cases during a given year and all health care resources used for prevention, treatment and rehabilitation, plus other resources used (formal and informal care) or loss of labor productivity

within that year as a consequence of the illness considered. Prevalence-based cost-of-illness analysis has the advantage of incorporating measurements of total annual healthcare expenditure, which is particularly relevant for chronic conditions such as JIA that require long-term treatment. In this context, a bottom-up costing approach was used to estimate total and average annual costs [5].

Data on resource utilization were collected for each patient. The resources used were multiplied by unit costs to estimate the annual cost per patient, with 2012 as the reference year.

Direct healthcare costs Direct costs were derived from healthcare utilization. The value of resources used by patients was calculated in terms of the relevant unit costs and the average cost per patient in the sample. Information about the number of hospital admissions was obtained from the questionnaires.

Data for the volume of outpatient care (rehabilitation, medical tests and examinations, visits to health professionals, and home medical care) and the number of emergency visits were obtained from the questionnaires. Unit costs that were obtained from different sources and healthcare cost databases (see Supplementary Annex 2) were then multiplied by the units of each resource used. Information regarding the medications used by patients with JIA was obtained from the questionnaires. The cost of drugs used by patients was calculated by determining the daily cost for each of the products used (based on the cost of each pack dispensed and the dose used) and then multiplying by duration of use. When no information concerning the number of units per pack was available, we assumed the largest pack-size was dispensed. The costs of prescription drugs used were obtained from the list of approved drugs in the different countries (see Supplementary Annex 2).

Information concerning the use of orthopedic devices and healthcare-related transportation was obtained from the questionnaires. The costs of orthopedic devices were obtained from different distribution firms.

Direct non-health care costs Informal care is defined as the performance of tasks by non-professionals that help maintain or enhance patient independence. Informal services are therefore defined as the group of tasks or care provided by non-professional caregivers, who are often relatives but may also be friends or neighbors. Information about informal care was obtained from the questionnaires, specifically from the items concerning the time spent helping the patient with his or her basic activities of daily living and the time spent helping with necessary instrumental activities of daily living (recall method). As a conservative criterion, and for preventing conjoint production, we have censored the time of care to a maximum of 16 h per day (112 h per week) when the time of care reported exceeded this figure.

The approach used to value the care hours was the proxy good method, which values time as an output. This method values the care provided by the informal caregiver considering that if he/she did not provide these services, their presence would have to be substituted by another person who could provide them [6]. Therefore, we took into consideration the question of how much it would cost to take on said substitution or replacement by hiring a professional caregiver [7].

Information on formal paid care provided by professional caregivers and other social services was obtained from the questionnaires and comes under the category of social services. Data on unit costs were provided by different sources (see Supplementary Annex 2).

Loss of labor productivity Data on loss of labor productivity were obtained from physical units converted into monetary units with a human capital-based approach [8]. According to human capital theory, the average earnings (gross wages) of a worker can be considered a good proxy for labor productivity losses. Therefore, our calculations were based on average gross wage figures in the Wage Structure Surveys by the National Statistics Institutes of the participating countries. Annual losses of labor productivity were estimated for the year 2012.

Patient and caregiver outcomes Patient and caregiver outcomes were obtained by means of self-administered questionnaires such as the EQ-5D, the Barthel index, and Zarit burden interview. The EQ-5D is a simple generic instrument developed by a multidisciplinary group of researchers [9]. This questionnaire has been validated in many countries in Europe, and is commonly used in economic evaluation and health technology assessment. There are five dimensions in the EQ-5D covering the areas of mobility, self-care, everyday activities, pain/discomfort, and anxiety/depression. A total of 245 possible health states can be defined in this way. Evaluations of these health states have been reported for the general population [9]. The values or utilities are indicated on a scale on which death has a value of 0 and perfect health a value of 1, with negative values being possible.

The Barthel index is a widely used tool for the assessment of disability and measures the ability of a person to perform ten basic activities of daily living, providing a quantitative estimate of the subject's degree of dependence [10, 11]. It is easy to apply, has a high degree of reliability and validity, is capable of detecting changes, and is easy to interpret. The Barthel index is recommended as the instrument of choice for measuring physical disability, both in clinical practice and public health research. A score of 91–99 shows mild dependence, 61–90 moderate

Table 1 Characteristics of the study participants

	Bulgaria	France	Germany	Italy	Sweden	UK
Patients						
No of responses	1	4	67	33	34	23
Mean age (SD)	5.0 (NA)	6.5 (3.9)	13.1 (7.2)	10.5 (4.6)	14.5 (7.9)	21.4 (16.8)
Mean age at diagnosis, years (SD)	5.0 (NA)	4.3 (4.7)	8.8 (6.3)	4.2 (4.0)	7.7 (5.7)	5.2 (4.4)
Female (%)	0 (0)	1 (25)	47 (70.1)	26 (78.8)	26 (76.5)	18 (78.3)
Informal caregivers						
No of responses	1	2	16	9	12	8
Mean age (SD)	33.0 (NA)	47.0 (4.2)	34.5 (13.1)	41.7 (11.3)	37.6 (10.0)	43.1 (9.7)
Female (%)	1 (100)	1 (50.0)	13 (81.3)	6 (66.7)	11 (91.7)	7 (87.5)
Relationship to patient						
Parent to the patient	0	0	14	0	1	1
Other relative to the patient	1	2	2	8	11	6
Partner or other	0	0	0	1	0	0
Informal caregivers, hours per a week (SD)	0.0 (NA)	15.8 (22.3)	52.0 (41.1)	29.3 (26.8)	22.9 (32.8)	25.3 (23.8)
Health outcomes						
Utilities adult patients (SD)	NA	NA	0.729 (0.139)	NA	0.642 (0.128)	0.262 (0.239)
Utilities caregivers (SD)	0.649 (NA)	0.377 (NA)	0.745 (0.259)	0.799 (0.144)	0.594 (0.105)	0.663 (0.367)
VAS adult patients (SD)	NA	NA	60.2 (19.2)	NA	56.1 (18.6)	49.0 (12.4)
VAS caregivers (SD)	50.0 (NA)	65.0 (NA)	71.6 (20.2)	78.3 (17.1)	69.8 (15.6)	67.1 (26.1)
Barthel index (patients) (SD)[a]	NA	97.5 (3.5)	93.4 (13.1)	97.2 (7.9)	89.3 (14.3)	80.9 (18.1)
Zarit scale (caregivers) (SD)	NA	50.0 (8.5)	24.6 (11.9)	16.4 (6.7)	30.9 (15.4)	22.9 (6.6)

[a] Barthel scores for Sweden and UK were re-escalated from 20-point scale to 100-point scale

dependence, 21–60 severe dependence, and <20 complete dependence [11].

Caregivers also completed the Zarit Burden Interview (22-item version), which measures the subjective burden among caregivers. Each item is a statement which the caregiver is asked to respond to using a 5-point scale, with options ranging from 0 (never) to 4 (nearly always) [12]. The total score ranges from 0 to 88, with scores under 21 corresponding to little or no burden and scores over 61 to severe burden.

Results

One hundred and sixty-two questionnaires from six countries were collected within the study. The largest number of questionnaires (67) was obtained from Germany. Italy and Sweden contributed equally to the total sample, providing 33 and 34 filled out questionnaires, respectively. The rest were obtained from the UK (23), France (four), and Bulgaria (one). The latter was excluded from further analysis due to the low response rate.

The resultant total sample consisted of 161 patients with JIA. The major part of the sample was children and adolescents (78 %) with a mean age of 14 years. Comparison between countries of mean ages and numbers of adults showed that the samples from France and Italy consisted only of children and patients in the UK sample were, on average, older than those from the other countries.

In contrast to the age of the patients, gender distribution in the samples did not significantly vary across the countries, with females accounting for 70.1 to 78.8 % in the total sample. The sample from France was an exception and contained only one female participant (25 %).

The overall sample also included the responses of 47 informal caregivers. Response rate varied across the countries, with the largest number of responses obtained from Germany (16), followed by Sweden (12), Italy (nine), the UK (eight), and France (two). The age of the caregivers ranged from 34.5 (Germany) to 47.0 (France), with a mean of 38.8 years. The share of female carers varied from 50.0 % in France to 91.7 % in Sweden. In total, 16 caregivers were parents and 29 were relatives. The amount of care provided ranged from 16 h a week in France to 52 in Germany, with the average being 34 h per week. Table 1 summarizes the samples obtained from each country.

We quantified HRQOL for patients with JIA and for non-professional caregivers using different approaches. Table 1 summarizes the resultant estimates.

Estimates of the patients' HRQOL calculated using the EQ-5D instrument (TTO tariff) differed among Germany, Sweden, and the UK. Although patients' HRQOL showed relatively high values in the German (0.729) and the

Table 2 Average annual costs per patient, all patients (2012, €)

Costs € 2012	Bulgaria		France		Germany		Italy		Sweden		UK	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Drugs	0	NA	6585	7521	6227	9044	15,522	29,368	11,524	12,410	6667	9206
Medical tests	49	NA	397	239	386	343	152	264	986	1503	2493	2662
Medical visits	427	NA	3073	4170	3919	3771	1681	1609	7770	8582	4169	3206
Hospitalizations	2262	NA	974	1948	5331	6278	3454	6000	1310	2387	1047	2962
Health material	0	NA	40	79	227	1022	0	0	47	830	114	162
Healthcare transport	21	NA	0	0	70	394	0	0	76	262	19	91
Direct healthcare costs	2759	NA	11,068	3663	16,161	12,705	20,808	34,092	22,138	17,245	14,508	14,877
Professional carer	0	NA	0	0	20	165	0	0	0	0	597	2546
Non-healthcare transport	91	NA	219	320	249	278	187	319	630	719	75	143
Social services	0	NA	0	0	1210	6599	26	146	3772	8928	50	241
Direct non-healthcare formal costs	91	NA	219	320	1479	6593	212	337	4402	9442	722	2532
Main informal carer	0	NA	4106	8213	8420	20,144	4043	9533	7081	19,228	5661	11,722
Other informal carers	0	NA	3520	7039	1483	6272	3583	9355	2673	7360	1940	9027
Direct non-healthcare informal costs	0	NA	7626	15,252	9903	24,271	7625	18,436	9753	25,999	7601	18,703
Direct non-healthcare costs	91	NA	7845	15,157	11,382	24,989	7837	18,437	14,155	30,405	8323	18,665
Direct costs	2850	NA	18,913	12,277	27,543	28,022	28,645	42,218	36,293	40,737	22,831	24,728
Sick leave	0	NA	0	0	91	465	0	0	103	599	190	513
Early retirement	0	NA	0	0	0	0	0	0	0	0	8525	14,673
Labor productivity losses patients	0	NA	0	0	91	465	0	0	103	599	8715	14,566
Total costs	2850	NA	18,913	12,277	27,634	28,008	28,645	42,218	36,396	40,742	31,546	28,568

Swedish (0.642) samples, variating inconsiderably from each other, the UK patients' HRQOL took a significantly lower value of 0.262.

Similarly to the patients with JIA, the caregivers were seen to have quality of life below 1.0 value, however, comparison between the estimates of the patients' HRQOL and the caregivers' HRQOL brought no clear inference about the existence of correlation between them. Considering the samples separately, the caregivers' HRQOL estimate obtained in the UK (0.663) was considerably higher than the patients' HRQOL (0.262); in Germany, it minimally differed from the patients' one, being 0.016 units higher (0.745); in Sweden, on opposite it was slightly lower, and took a value of 0.594. Overall, among all countries in the study, the estimates of the caregivers' HRQOL ranged from 0.594 to 0.799, with exception of the French sample, which showed the lowest value (0.377).

HRQOL estimates obtained over the total sample using EQ-5D showed a mean value of 0.56 for the patients and 0.7 for the caregivers.

Estimates of HRQOL calculated with the VAS scale showed a different pattern. According to this scale, the patients' quality of life was seen to considerably lower than that of the caregivers across all samples.

Additionally, HRQOL was analyzed applying the Barthel index and the Zarit scale. The Barthel index yielded scores 80.9 (UK) to 97.5 (France) with an average for the total sample of 91.5. The ranges in the Zarit scale values varied from country to country, from 16.4 in Italy to 50.0 in France, with a mean of 25.1 for the total sample.

Annual costs Resultant annual total costs varied from €18,913 in France to €36,396 in Sweden, with a mean for the total sample of €30,034 (±SD 33,945) per patient. The largest cost fraction was direct healthcare costs, taking up over 50 % of the total cost across all countries except the UK. Although the direct healthcare costs fraction for the UK was 46 %, they had the highest percentage of lost productivity (27.6 %), due to having the largest number of adults in the sample. The percentage of direct non-healthcare costs varied from country to country, with the lowest in the UK sample (26 %) and the highest in the French sample (41.48 %). Table 2 summarizes total annual costs and costs in each cost fraction for each country.

Although the structure of the direct healthcare differed across the countries, expenditures for medication constituted the largest share for all samples. The next largest fraction differed from country to country, but was either medical visits or hospitalization. The UK sample had the largest share of aggregated expenses for healthcare

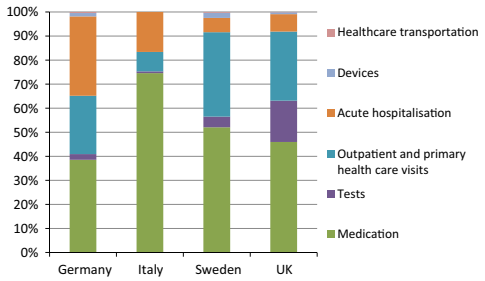

Fig. 1 Direct healthcare costs

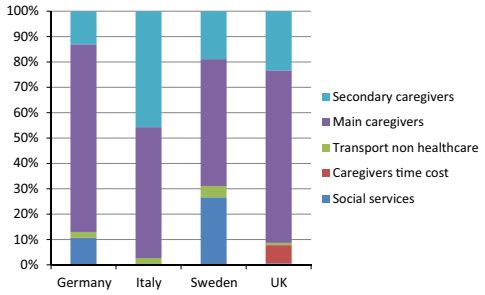

Fig. 2 Direct non-healthcare costs

transportation, health material, and medical tests (18 %). The fractions of direct healthcare costs are illustrated in Fig. 1.

The main part of direct non-healthcare costs in all countries was for informal caregivers plus professional carers, ranging from 68.90 % in Sweden to 98.49 % in the UK. Another direct non-healthcare cost fraction, social services, showed no similarities across the countries, ranging from 0 % in the French sample to 26.65 % in Sweden.

Among all fractions of direct non-healthcare costs, transportation costs were the smallest, varying from 0.9 % (UK) to 4.45 % (Sweden). The direct non-healthcare costs are presented in Fig. 2.

When looking specifically at the costs incurred by adults (36 patients), the data were included in the analysis based on the sample sizes of the UK, France, Germany, Sweden, and Italy. Mean annual costs ranged from €15,201 per patient in Sweden to €40,940 in the UK (Table 3). Direct healthcare costs ranged from €10,504 per patient in Sweden to €20,985 in Germany and direct non-healthcare costs ranged from €1933 per patient in Germany to €5116 in the UK (Table 3). Loss of labor productivity costs ranged from €349 per patient in Sweden to €20,045 in the UK (Table 3).

For pediatric patients, 125 were included in the analysis. Mean annual costs ranged from €18,913 per patient in France to €45,227 in Sweden (Table 4). Direct healthcare costs ranged from €11,068 per patient in France to €26,985 in Sweden and direct non-healthcare costs ranged from €7837 per patient in Italy to €18,242 in Sweden (Table 4).

Discussion

In this study, we analyzed JIA-related healthcare costs and quality of life based on the samples obtained from six European countries. We estimated direct healthcare and non-healthcare costs and labor productivity losses and quantified HRQOL for patients with JIA and their non-professional caregivers. We compared differences between the countries and analyzed the collected sample as a whole.

The study populations included show some heteroscedasticity in terms of the sample size and age. Given that the number of participants in Italy, Sweden, and the UK was similar, the sample from France provided four questionnaires and the sample obtained for Germany had the largest size, estimates of JIA-related costs and HRQOL obtained for the total sample are driven by the German study population.

Furthermore, the age structure of the UK sample significantly differed from other countries. The main difference lies in the number of adults who participated in the survey. In the UK sample, the number of adults was almost twice that of any other country, whereas the French and Italian samples contained no adult population. In contrast to the age structure, the gender ratio did not significantly vary from country to country, except for France, where the sample only consisted of four patients, with one female.

While there was a moderate difference in the mean age between Italy, Germany, and Sweden, the gap between the UK and the other countries ranged from 6.9 to 10.9 years. This can be explained by the differences in the number of adult participants, with adults making up 43.48 % of the UK sample but comparatively less of the samples from Germany and Sweden, with 23.88 and 29.41 %, respectively. In comparison with these countries, the samples obtained from Italy and France contain a younger population with a mean age of 10.5 and 6.6 years, respectively. The difference in the estimates of the mean age ranged from 4 to 8 years, determined by the absence of adult patients in the French and Italian samples.

Weekly amount of care and relationship between informal caregivers and the patients also varied from country to country. The samples from Italy, Sweden, and the UK reported the average amount of care to be from 22.9 to 29.3 h per week. These samples also showed that patients receive mostly non-parental care. The share of the informal caregivers with other relationships to patients ranges from 75 to

Table 3 Average annual costs per adult patient, adult patients (2012, €)

Costs € 2012	UK ($N = 10$)	France ($N = 0$)	Germany ($N = 16$)	Sweden ($N = 10$)	Italy ($N = 0$)
Drugs	6313	–	11,542	8	–
Medical tests	3226	–	278	1583	–
Medical visits	4102	–	5504	7033	–
Hospitalizations	1887	–	3563	1343	–
Health material	207	–	85	414	–
Healthcare transport	43	–	13	124	–
Direct healthcare costs	15,779	–	20,985	10,504	–
Professional carer	1372	–	0	0	–
Non-healthcare transport	110	–	333	474	–
Social services	0	–	8	2737	–
Main informal carer	3633	–	1592	1137	–
Other informal carers	0	–	0	0	–
Direct non-healthcare costs	5116	–	1933	4348	–
Direct costs	20,895	–	22,917	14,852	–
Productivity loss patients	437	–	383	349	–
Early retirement patients	19,609	–	0	0	–
Indirect costs	20,045	–	383	349	–
Total costs	40,940	–	23,300	15,201	–

Table 4 Average annual costs per pediatric patient, pediatric patients (2012, €)

Costs € 2012	UK ($N = 13$)	France ($N = 4$)	Germany ($N = 51$)	Sweden ($N = 24$)	Italy ($N = 33$)
Drugs	6939	6585	4560	16,322	15,522
Medical tests	1929	397	420	737	152
Medical visits	4220	3073	3422	8077	1681
Hospitalizations	401	974	5886	1296	3454
Health material	42	40	271	496	0
Healthcare transport	0	0	88	57	0
Direct healthcare costs	13,531	11,068	14,648	26,985	20,808
Professional carer	0	0	27	0	0
Non-healthcare transport	48	219	223	694	187
Social services	89	0	1587	4204	26
Main informal carer	7220	4106	10,562	9557	4042
Other informal carers	3432	3520	1948	3786	3583
Direct non-healthcare costs	10,789	7845	14,346	18,242	7837
Direct costs	24,320	18,913	28,994	45,227	28,645
Productivity loss patients	0	0	0	0	0
Early retirement patients	0	0	0	0	0
Indirect costs	0	0	0	0	0
Total costs	24,320	18,913	28,994	45,227	28,645

100 %. Germany stands apart from these countries, reporting significantly larger estimates for both the share of parental care (87.5 %) and the weekly amount of care (52 h), which results in considerably higher time expenditure.

We found that JIA had a significant impact on the HRQOL of patients and their caregivers regardless of the country. In adults, direct healthcare costs, especially drugs, hospitalizations and medical visits, represented the vast majority of costs, while in children, drugs, hospitalizations, medical visits, and direct non-healthcare informal costs, i.e., caregivers' time, were predominant.

A study carried out by the London School of Economics and Political Science within the BURQOL-RD project [13] identified eight costing studies, from which only three

examined labor productivity losses in addition to direct costs [14–16]. The mean annual cost per patient was estimated to be between €3471 [14] and €4663 [15], with estimates that a very small proportion of the population (12 %) is responsible for 80 % of the overall costs incurred [14].

The estimates of average annual total costs per patient ranged in our study range from €18,913 to €36,396 and are significantly higher than the reported estimates. The main reason for this difference is that, in contrast to those studies, we included costs for non-professional caregivers in the cost calculation. In our analysis, costs for non-professional care make up a substantial fraction (68.9–98.5 %) of the direct non-healthcare costs. Subtracting these costs, the direct healthcare costs calculated in our analysis still show a considerable difference compared with previous studies. In Germany, the average total costs per patient excluding costs for non-professional caregivers are €17,731, which is still significantly higher than the estimates (€4663) obtained by Minden et al. for 2008 [15]. The main difference in the results is down to differences in the medication applied and length of hospital stay. In the study by Minden et al., the proportion of patients treated with biologics was 6 %, compared to 53.73 % in the BURQOL-RD survey. In Germany, the annual costs for biologics ranged from €5,223.33 to €19,720.39 per patient, so the increasing number of patients receiving biologics therefore has a high impact on the mean total costs. The average length of hospital stay also significantly differs between the BURQOL-RD (10.79 days) and the study by Minden et al. (4.34) days [15].

Three patterns were seen when comparing structures of direct healthcare costs across the countries. First, medication costs took up the largest share in all samples. Second, in the German and Italian samples, hospitalizations made up the second largest cost fraction followed by medical visits, with the remaining fractions contributing less to the direct costs. Third, in contrast to Germany and Italy, costs for medical visits in France, Sweden, and the UK were higher than those for hospitalizations. Additionally, in the UK sample, the costs for medical tests took up a considerable share.

In the structure of the direct non-healthcare costs, two major fractions were observed for all countries: costs for main informal caregivers; and costs for the other informal caregivers, with the former being the largest. Costs for social services are the largest observed for the Swedish sample and costs for professional carers the largest for the UK. Transport costs have the smallest share in the direct non-healthcare costs.

Although in the French, German, Italian, and Swedish samples the second largest part is direct non-healthcare costs, in the UK, the cost of loss of labor productivity makes up a considerable share of the total. The UK sample contains a relatively large number of adults and in this sample, productivity losses are mainly caused by early retirement; however, due to the small study sample, it is difficult to derive a valid inference about stable causality.

A review of HRQOL instruments used for rare diseases was carried out within the BURQOL-RD project by the Swedish Institute for Health Economics (IHE) [17]. Thirty articles studied HRQOL in patients with JIA, whereof the majority (24 articles) used generic measurements, such as the Childhood Health Assessment Questionnaire (CHAQ), SF-36 or EQ-5D; with the latter two showing impairment compared to the general population [18–20]. Only four articles applied a disease-specific questionnaire, either the Juvenile Arthritis Quality of Life Questionnaire (JAQQ) [21–23] or Arthritis Impact Measurement Scales [19].

In this study, we used a range of instruments to quantify health-related quality of life for patients with JIA and non-professional caregivers: the EQ-5D index score and the VAS scale were used to measure HRQOL in both patients and caregivers; the Barthel index was applied to patients only; and the Zarit scale was used for caregivers only.

The EQ-5D index score estimates HRQOL obtained for the patients were close to the middle of the possible range and lower than for caregivers. The estimates obtained with the VAS scale similarly showed lower values of the patients' HRQOL as those of the caregivers, supporting the results obtained using the EQ-5D index. Both instruments indicated a reduction in health status for patients with JIA. Additionally, the average Barthel index score of 91.5 implied the presence of mild dependence, however, this could be caused by inclusion of children in the calculations.

Comparison of the results among the countries indicated contrastingly low HRQOL estimates for patients in the UK sample. The population structure of this sample differed from the German and the Swedish samples, presenting older adult population of 38.5 years old on average, whereas the German and Swedish samples had younger adults with an average age of 22.8 and 24.2 years.

The resultant difference in the estimates of HRQOL might point to an age bias in average HRQOL; however, the small sample size made it difficult to provide a clear statement about a causal relationship between these variables.

Estimates of HRQOL for JIA-related non-professional caregivers indicated the existence of a caregiving burden. According to the mean Zarit score of 25.1, the burden is, on average, small. On average, the highest burden of 50.0 was reported in the French study sample, corresponding to the lowest EQ-5D utility for caregivers. The lowest burden of 16.4 was in the Italian study sample, which also corresponded to the highest EQ-5D index score estimate for caregivers.

Conclusions

The results of the BURQOL-RD project confirm the existence of socio-economic burden caused by juvenile idiopathic arthritis in Europe. Although JIA-related healthcare and non-healthcare costs vary across the countries, the estimated magnitudes of costs are high. Compared with previous studies, our results show a remarkable increase in annual healthcare costs for JIA patients. Reasons for the increase are the inclusion of non-professional caregiver costs, a wider use of biologics, and longer hospital stays. The related quality of life worsens for both patients and non-professional caregivers. Patients with JIA show a medium impairment in health status and caregivers have a life burden. The estimates of HRQOL also varied across the countries. Variation in the age structures is seen to be a possible reason for these differences.

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Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflicts of interest.

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APPENDIX I: BURQOL-RD RESEARCH NETWORK

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- University Paris Est (France): Karine Chevreul, Karen Brigham
- Universita Commerciale “Luigi Bocconi” (Italy): Giovanni Fattore, Marianna Cavazza

Annex II: Unit costs sources

Bulgaria

- National Health Insurance Fund (all direct healthcare costs) - http://www.nhif.bg
- National Statistical Institute - http://www.nsi.bg

France

- Base des médicaments et informations tarifaires. Available from: http://www.codage.ext.cnamts.fr/codif/bdm_it/index_presentation.php?p_site=AMELI
- Liste des produits et prestations. Available from: http://www.codage.ext.cnamts.fr/codif/tips/index_presentation.php?p_site=AMELI
- Classification commune des actes médicaux. Available from: http://www.ameli.fr/accueil-de-la-ccam/index.php
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- Echelle nationale coûts par GHM. Available from: http://www.atih.sante.fr/?id=000370000AFF
- Institut national de la statistique et des études économiques. Available from: http://www.insee.fr/fr/

Germany

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Hungary

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Italy

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Spain

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Sweden

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UK

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Modul 4

Age- and gender-based comorbidity categories in general practitioner and pulmonology patients with COPD

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Age- and gender-based comorbidity categories in general practitioner and pulmonology patients with COPD

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Chronic obstructive pulmonary disease (COPD) is a debilitating medical condition often accompanied by multiple chronic conditions. COPD is more frequent among older adults and affects both genders. The aim of the current cross-sectional survey was to characterize chronic comorbidities stratified by gender and age among patients with COPD under the care of general practitioners (GP) and pulmonologists, using real-world patient data. A total of 7966 COPD patients (women: 45%) with more than 5 years of the observation period in the practice were examined using 60 different Chronic comorbid conditions (CCC) and Elixhauser measures. More than 9 in 10 patients had at least one, and 51.7% had more than three comorbidities. No gender difference was found in the number of comorbidities. However, men had higher Elixhauser-van Walraven index scores than women, and the types of comorbidities differed by gender. An increasing number of comorbidities was seen with aging but the patients in their 30s and 40s also had a high number of comorbidities. Moreover, GP patients had a higher number and a wider array of documented comorbidities than pulmonology patients did. Psychological comorbidities were common in all patients, but particularly among younger patients. These findings around gender- and age-stratified comorbidities under the care of GPs and pulmonologists have implications for the choice of data provenience for decision-making analysis and treatment selection and success.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD), characterized by chronic obstruction of lung airflow that interferes with normal breathing, claims millions of lives each year and is the fourth leading cause of mortality worldwide[1,2]. COPD used to be more common in men; however, because of increased tobacco use and the higher risk of exposure to indoor air pollution among women, the disease now affects both men and women almost equally[2]. Additionally, COPD is more common among the elderly population as COPD symptoms develop slowly and become apparent during middle age[2,3]. Considering one in six people will be over the age of 65 by 2050[4], the aging of the general population may further increase the burden of COPD.

COPD patients often have a multitude of other chronic conditions that can influence the prognosis of COPD and complicate the disease management[5]. Patients with COPD often die prematurely after suffering for many years due to COPD or its comorbid conditions[1]. These comorbid conditions increase economic burdens by directly increasing medical costs associated with hospitalization and service utilization and indirectly via early retirement or inability to work[6,7]. Recently, multiple studies have further enhanced our understanding of COPD and associated comorbidities[8–12], and some highlighted the potential underlying pathophysiology of COPD, the mechanism of systemic inflammation[13,14]. These studies of comorbidities are crucial because thoroughly understanding the nature and pattern of comorbidity is the foundation for physicians to provide broad yet appropriately targeted and prioritized treatments to enhance the COPD treatment outcome.

While past comorbidity studies have revealed invaluable information about the association and potential mechanism of comorbidities, thorough documentation of COPD comorbidities using routine real-world data in primary care settings is still scarce. Moreover, previous studies either have examined a small number of chronic conditions or did not examine gender differences[8–12]. Therefore, our study aimed to examine the comorbidities stratified by gender and age among primary care patients with COPD using routine care data from the electronic patient records of general practice and pulmonology settings. Our goal is to contribute to the creation of a road map of personalized holistic treatment choices, by outlining the gender- and age-specific comorbidities among patients with COPD.

METHODS

Study design

The current study was a cross-sectional survey using primary care data of the German BeoNet Register-Database (BNR). The BNR is a compilation of all routinely documented information from primary care electronic patient records from general practitioners (GPs) and pulmonologists participating in the network. It comprises a retrospective dataset since the practice used electronic files and the database is updated weekly. Only completely anonymized data are available for research purposes. In Germany, all physicians in outpatient practices are considered primary care physicians because patients have direct access to any physician without a referral and regardless of their specialty[15]. Therefore, the patient records from both GP and pulmonology practices were included in the study. Written informed consent from patients was not

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required, as the analyses were performed on a de-identified dataset out of the Registry database. The study was approved by the Medizinische Hochschule Hannover (MHH) ethics committee.

Study patients

Female and male patients aged 20 years and older with physician-diagnosed COPD were included in the analyses. Physician-diagnosed COPD was identified by having two documented diagnostic codes of J44 following the International Statistical Classification of Diseases (ICD-10)[16,17], and one of which was a permanent diagnosis of COPD. Moreover, patients must have been under observation at least for 5 years, so that the cumulated comorbidities reflect their overall health status. Exclusion criteria were age <20 years old, and/or missing data on major variables such as gender and age. The detailed patient selection process is presented as a flowchart in the Supplementary Document (Supplementary Fig. 1). The patients were stratified into seven age groups based on their age at their last visit: 20s, 30s, 40s, 50s, 60s, 70s, and 80s+ group. Overall comorbidity is stratified and examined by gender and age group.

The 10-year index period analysis. We examined comorbidity occurrence during a 10-year index period, 5 years before and 5 years after the index date. The index date was defined as the time of the first office visit with documented COPD. Based on the age of the patients at the index date, three groups were formed and examined: the <45, 45–64, and ≥65 years of index age groups. For this analysis, the patients who had not been with the practice for more than 10 years (5 years before and after the index date) were excluded.

Comorbidity measures

All ICD codes of each patient entered in the database were examined. Sixty chronic comorbid conditions (CCC) were created by searching and re-coding individual ICD-10 codes into different disease categories corresponding to the classification of Calderón-Larrañaga et al.[18]. Disease category names and codes were retained without any alterations according to the original publication. However, for the purposes of this study, ICD-10 code J44 was excluded from the category named "COPD, emphysema, chronic bronchitis." The total number of CCC and frequency of 60 categories were examined. In addition, 30 Elixhauser comorbid conditions were generated[19,20]. Although Elixhauser comorbidity includes a smaller number of comorbidity than CCC, the Elixhauser measure was included for its summation scores and index scores based on the van Walraven (vW) algorithm. Elixhauser-vW index scores have been linked to mortality rates and provide additional information, which cannot be assessed using summation scores of each disease category alone[21–27]. Elixhauser-vW index scores were calculated by weighting individual comorbidity categories[21]. The J44 diagnosis was excluded from the total number of comorbidity but not from the Elixhauser-vW index score to adhere to the original algorithm. For the 10-year index period analyses, only the first documentation of each comorbidity was considered.

Data and statistical analyses

The BNR-database was accessed in September 2020. All available medical records of patients with permanent COPD diagnoses were extracted along with patient demographic information and the documented dates of their practice visits. In the first data processing step, the formats were standardized. Subsequently, the variables needed for the inclusion and exclusion criteria were created. Finally, the diagnosis data were reduced to the ICD codes required by the employed methods. The software R (R Core Team, 2020) was used for this process.

Descriptive statistics are presented as means and standard deviations (SD) or absolute numbers and percentages. Given the robustness of parametric tests with large sample sizes, independent *t*-tests were used to compare demographic gender differences (χ^2 test for categorical variables) and analysis of variance (ANOVA) was used to compare the group differences. The Bonferroni post hoc tests were conducted to follow-up on age group differences. The statistical significance level was set at $p < 0.05$ (two-tailed), and all data were analyzed using the SPSS statistical software package (SPSS, version 26); SPSS and Excel (Microsoft Office Professional Plus 2016) were utilized to create figures.

Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this article.

RESULTS

Sample characteristics

A total of 7966 patients with COPD from 20 GPs and six pulmonologists were included in the study. The 20s age group was small (female = 6; male = 3) and thus excluded from further analyses. Men had a longer observation period in the practice after the first documentation of COPD compared to women ($p < 0.01$). However, the total observation years in practice did not differ by gender. There were more men in the 70s group than women ($p < 0.05$), but no other age groups differed by gender. See Table 1.

Comorbidity by gender and age group

Comorbidity measures were analyzed using separate 2 × 6 factorial ANOVAs (Gender × Age group). Women and men did not differ in the mean number (M(SD)) of comorbidities assessed by chronic comorbid conditions (CCC) (women: 4.03 (5.40) and men: 4.01 (5.03), $p = 0.87$) or Elixhauser (women: 1.98 (2.31) and men: 2.04 (2.30), $p = 0.67$). In general, older age groups had more comorbidities than the younger groups in both comorbidity measures (both $p < 0.001$). Moreover, this age difference in the prevalence was seen in both genders (all significant at $p < 0.001$) (see Fig. 1a, b). The Bonferroni post hoc tests of age group comparisons showed that for CCC, the 80s group had significantly more comorbidities than all other age groups, and furthermore the 70s group was significantly different from the 40s and 50s groups. For Elixhauser comorbidities, the 80s and 70s groups had a significantly higher number of comorbidities than their respective younger groups, while the 60s group differed significantly from the 40s and the 50s group. For both CCC and Elixhauser, the 30s, 40s, and 50s groups did not significantly differ from each other. No interaction term existed between gender and age. The *p* values from Bonferroni tests are provided in the supplementary document (Supplementary Table 1).

Elixhauser-van Walraven (vW) index scores showed significant effects of gender ($p < 0.01$) and age group ($p < 0.001$). Despite having a similar number of Elixhauser conditions, men had significantly higher mean Elixhauser-vW index scores than women (men: 5.80 (6.97) and women: 5.06 (6.32), $p < 0.01$) (see Fig. 1c). A sensitivity analysis of Elixhauser-vW index scores, excluding J44 diagnosis, also confirmed the finding of the primary analysis that men had significantly higher mean Elixhauser-vW index scores than women (men: 4.33 (7.25) and women: 3.73 (6.55), $p < 0.05$). According to the Bonferroni test of the Elixhauser-vW index score, the 80s group had significantly higher scores than all the other age groups; the 70s had significantly higher index scores compared to all the other younger age groups besides the 30s group; and the 60s group had a significantly higher index score

Table 1. Characteristics of 7957 COPD patients by gender.

Variable	*n* (%) or mean (SD)		
	Female ($n = 3573$, 44.9%)	Male ($n = 4384$, 55.1%)	*p*
Age during the last visit (years)	70.1 (11.9)	70.5 (11.3)	0.12
Age group			<0.05
30s	34 (1.0%)	40 (0.9%)	
40s	145 (4.1%)	138 (3.1%)	
50s	493 (13.8%)	584 (13.3%)	
60s	993 (27.8%)	1155 (26.3%)	
70s	1048 (29.3%)	1430 (32.6%)	
80s+	860 (24.1%)	1037 (23.7%)	
GP (%)/pulmonologist (%)	1021 (28.5%)/2558 (71.5%)	1172 (26.7%)/3215 (73.3%)	0.07
Age of 1st COPD documentation	61.2 (12.7)	61.2 (11.8)	0.99
Duration in practice since 1st COPD documentation (years)	8.9 (6.4)	9.3 (6.5)	<0.01
Observation years in practice	13.9 (6.7)	13.7 (6.6)	0.31

P values are based on an independent *t*-test or a χ^2 test.

compared to the 40s and 50s. Similar to the findings from CCC and Elixhauser scores, the 30s, 40s, and 50s groups did not significantly differ from each other on the Elixhauser-vW index score. There was no significant gender and age group interaction.

Examination of the Elixhauser-vW index algorithm and the weight values showed that women were diagnosed more frequently with deficiency anemia and depression than men, and these conditions have negative weights of −2 and −3, respectively. In contrast, men were diagnosed more frequently than women with the conditions of positive weights for the algorithm: solid tumor without metastasis, cardiac arrhythmias, congestive heart failure, peripheral vascular disorder, and metastatic cancer (weights: 4, 5, 7, 2, and 12, respectively). Men did not have a higher frequency of any conditions that have negative weights compared to women. Detailed data are provided in the Supplementary Document (Supplementary Table 2).

Number of comorbidities by gender and age group differentiated by practice types

Whether the patient was from a GP or pulmonology practice had a significant impact on the number of comorbidities. A three-way ANOVA test was performed excluding the 30s group due to the small sample size in GP patients ($n = 13$). GP patients had a higher mean number of documented comorbidities than the pulmonology patients for all measures (CCC: 7.8 (8.5) and 2.6 (1.6); Elixhauser: 3.5 (3.7) and 1.5 (1.1), and Elixhauser-vW index score: (9.49 (10.6) and 3.96 (3.2), all significant at $p < 0.001$). Observation years differed by practice types (GP: 14.6 (7.1) vs Pulmonology 13.5 (6.4) years) but accounting for this difference statistically did not change the results. There was no gender difference in both CCC and Elixhauser. However, men had a significantly higher Elixhauser-vW index score than women in both practices (GP: men: 10.2 (11.1) and women: 8.7 (10.0), $p < 0.01$ and Pulmonology: men: 4.2 (3.4) and women: 3.6 (2.9), $p < 0.001$). See Fig. 2 and the Supplementary Document (Supplementary Table 3) for the corresponding data.

As the interaction terms between practice type and age groups were significant, the data were examined by practice type. In both practices, age groups differed in the number of comorbidities in CCC, Elixhauser, and Elixhauser-vW index scores. The Bonferroni post hoc tests of the age group comparisons are provided in the Supplementary Document (Supplementary Table 4).

CCC. Among GP patients, the 80s+ group was different from all other age groups. The 70s were only different from the 50s in the sample of GPs patients whereas the 70s in the pulmonologist sample differed from all other younger age groups. For pulmonology patients, the 80s+ group was different from the 40s, 50s, and 70s groups. The 40s group was different from all other groups but not from the 50s (see Fig. 2a).

Elixhauser. Among GP patients, the 80s+ group was different from all other age groups except the 70s group, and the 70s group was in addition only different from the 50s groups. For pulmonology patients, all age groups were distinctly different from each other except for the 80s+ to 70s.

Elixhauser-vW index score. Among GP patients, the 80s+ was different from all other groups except the 70s. The 70s group was also different from the 40s and 50s, and the 60s only differed from the 50s. Among pulmonology patients, the 80s and 70s, and 60s groups had higher index scores compared to all of their respective younger age groups.

Percent distribution of patients with comorbidities by gender and age group differentiated by practice types

From the entire COPD patient sample, only 8.5% had no comorbidities while 91.5% had at least one comorbidity. Of the 60 CCC categories, 17.5, 22.3, 19.4, 11.0, 6.2, 3.0, and 12.1% had one through ≥7 comorbidities, respectively. Overall, six diseases of the 60 categories were not documented among pulmonology patients while only one disease had no documentation in the GP patients. No gender difference was found in the percent distribution of the number of comorbid conditions. Figure 3 shows the percentage of patients with a number of comorbidities (0 through 7+) by age group combined across genders (excluding the 30s group due to the small sample size among GP patients). Among GP patients, overall 11.0% had 0 and 39.8% had more than 7 comorbidities, and among pulmonologist patients, it was 7.5% and 1.5%, respectively.

Type of comorbidities by gender and age group differentiated by practice types

For all patients, 12 out of the 60 CCC showed a prevalence greater than 10%, while 15 disease categories had a prevalence between 5 and <10%, and 20 conditions between 1 and <5%. Only 13

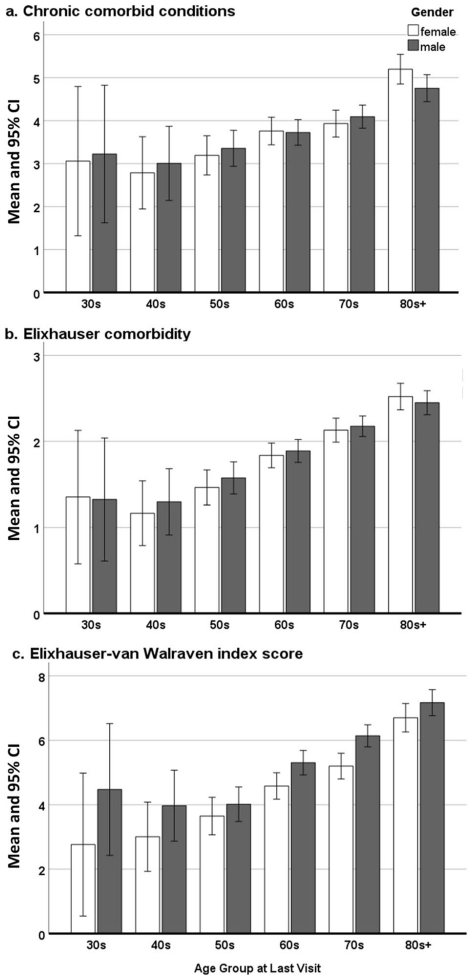

Fig. 1 Chronic comorbid conditions (CCC), Elixhauser, and Elixhauser-van Walraven index scores by gender and age group. Mean number of comorbidities with error bars representing 95% confidence intervals.

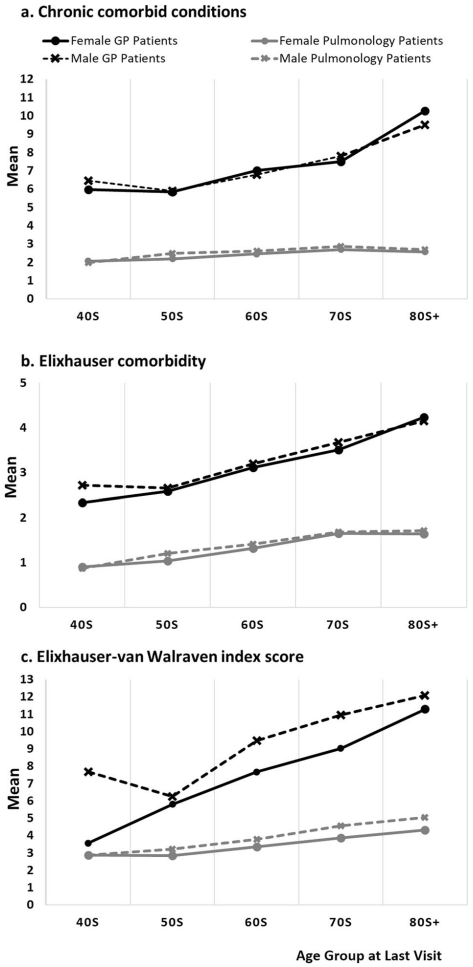

Fig. 2 Chronic comorbid conditions (CCC), Elixhauser, and Elixhauser-vW index by gender, age group, and practice type. Figures represent mean number of comorbidities for each age group separated by gender and practice type.

comorbidity categories showed less than a 1% prevalence. Table 2 displays the overall frequency of each comorbidity category by gender. Including all patients, the most frequently documented comorbidity among COPD patients was hypertension. Among the 60 CCC with a >10% frequency rate, men were documented significantly more often with other respiratory diseases, sleep disorders, ischemic heart diseases, diabetes, other psychiatric and behavioral diseases, and heart failure than women did. Women had more asthma, allergy, and esophagus, stomach, and duodenum diseases than men did.

Gender- and age group-specific comorbidities that had a >20% frequency for GP patients and pulmonology patients are presented in Fig. 4. Female patients in GP practice had 30 diseases with a frequency of more than 10% and male patients had 29 diseases (Fig. 4a, b). Sleep and psychological comorbidities were important. Among the top 10 comorbidities, men had sleep disorders (25.1%), and women had neurotic, stress-related, and somatoform diseases (26.1%). Depression and mood diseases were identified in both women (24.1%) and men (13.8%). The frequency of almost all disease categories increased with increasing age for both men and women. However, some diseases were documented more frequently in younger patients compared to older patients such as asthma, thyroid diseases, and neurotic stress-related and somatoform diseases. See Supplementary Document (Supplementary Table 5) for complete data.

In contrast to the GP patients, the pulmonology patients had fewer numbers of comorbidities documented with a frequency greater than 20%: women had four and men had five categories

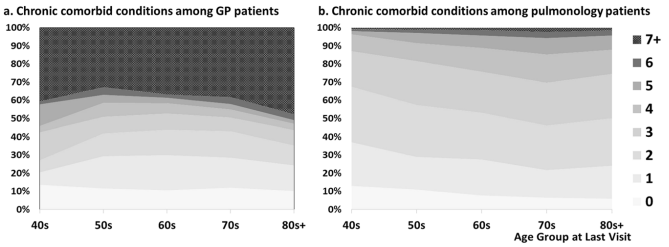

Fig. 3 Percent distribution of patients with a number of chronic comorbid conditions (CCC). Figures represent frequency of patients with a number of comorbidities, from 0 to 7 or more, for each age group separated by practice type.

(Fig. 4c, d). In both genders, nine comorbidities were documented with a frequency greater than 10%. Among pulmonology patients, the COPD, emphysema, chronic bronchitis category was most frequently observed in both genders. The frequency of most diseases increased with age.

Comorbidity during the 10-year COPD index period

After excluding patients who did not have continuous visitation records ±5 years of the first documentation of COPD, 432 GP and 548 pulmonology patients were included in the analysis. Table 3 shows the top 20 chronic comorbidities for the GP and the top 10 for the pulmonology patients by 3-index age groups (age at first COPD documentation <45, 45–64, and ≥65 years old) and over three index periods (Before: >5 years before the first COPD visit; Index Period: ±5 years; and After: >5 years).

GP Patients. The 3-index age groups of GP patients did not significantly differ by gender (women: <45: 20 (62.5%); 45–64: 89 (40.8%); and ≥65: 84 (46.2%)); however, the mean number of observation years was different among 3-index age groups (<45: 24.4 (6.1) years, 45–64: 22.67 (6.6), and >65: 21.4 (6.3), $p < 0.05$). The <45 index age group had 35 comorbidities with a >10% frequency rate, the 45–64 index age group had 40, and the ≥65 index age group had 41 across three index periods. However, the youngest index age group had a higher number of comorbidities with a >50% frequency than the other two index age groups (13 diseases in the <45, 5 in the 45–64, and 9 in the ≥65 group) (see Table 3). Among the diseases with a >50% frequency rate, in the <45 index age group, esophagus, stomach, and duodenum diseases were documented most frequently during the 10-year index period. They were followed by depression and mood diseases, and neurotic, stress-related and somatoform diseases. Among the 45–64 and ≥65 index age groups, hypertension was the most frequently documented comorbidity during the 10-year index period, and psychological comorbidities diseases did not exceed a 50% frequency rate as did in the younger group.

Pulmonology Patients. The 3-index age groups of pulmonology patients did not differ by gender (women: <45: 28 (57.1%); 45-64: 114 (43.8%); and ≥65: 120 (50.2%)). However, as was the case in the GP sample, the mean number of observation years varied within the 3-index age groups (<45: 22.2(4.9) years, 45-65: 22.1 (4.8), ≥65: 20.8 (4.8), $p < 0.01$). The <45 and 45–64 index age groups had nine disease categories with a >10% frequency rate, and ≥65 index age group had eight. Each index age group had only one comorbidity with a >50% frequency; asthma for the youngest index age group, and COPD, emphysema, and chronic bronchitis for the other two groups (see Table 3). Among the comorbidities with a frequency rate greater than 10% during the 10-year index period in pulmonology patients, other psychiatric and behavioral diseases were the only comorbidity that was most often documented during the index period in the <45 index age group. For the 45–64 index age group, (COPD), emphysema, chronic bronchitis, sleep disorders, and other psychiatric and behavioral disorders were most common; and for the >65 index age group, hypertension and other respiratory diseases were most common during the 10-year index period compared to the before or after periods. Other psychiatric and behavioral diseases category was documented more frequently during the 10-year index period than before or after periods combined in all 3-index age groups.

DISCUSSION

The present study examined gender- and age group-specific chronic comorbidities in primary care patients with COPD stratified by the medical practice type: GP and pulmonology practices. Our main findings were threefold. Firstly, the type of medical practice mattered in documented numbers and types of chronic comorbidities. Secondly, a gender difference was seen in the type of but not in the number of comorbid conditions. Lastly, although increasing age was associated with an increasing number of comorbidities, our younger groups of patients with COPD also displayed multiple comorbidities. Overall, less than 1 in 10 patients had no documented comorbidities, and 75% of the patients had two or more comorbidities.

GPs documented a higher number of and more heterogeneous comorbidities while pulmonologists documented comorbidities more specific to their specialty. This implies that compiled routine data of GP patients display a more complete picture of patients' health. Our data indicate that in pulmonology practices, diseases affecting other organs or systems other than the lungs are only scarcely documented in the patients' records. Under- and over-treatment of patients with COPD and comorbidities may result if there is a lack of information and communication about comorbid conditions between these practices and other medical specialists.

Despite having a more complete picture of the patients' health, primary care physicians report unique challenges of treating COPD due to the medical culture of prioritizing diseases and treating one disease at a time regardless of the reality that most patients suffer from multiple diseases simultaneously[28]. Acute conditions take precedence during unscheduled visits and other conditions such as heart diseases are prioritized during routine visits while the lack of awareness of and concern for COPD further hinders the care of patients with COPD, especially when GPs are pressured for time[28]. Fostering a more holistic approach to medical practice rather than prioritizing and allowing longer consultation durations with the corresponding remuneration can perhaps combat de-prioritization of COPD and enhance early detection of COPD, which could prevent the onset of some of the comorbidities and further improve the treatment of COPD in GP practices.

Examining comorbidities by gender in our study revealed no significant difference in the mean number of comorbidities documented; however, the type of comorbidity was gender-specific, and this difference contributed to the distinct Elixhauser-vW index scores. Men had higher Elixhauser-vW index scores than

Table 2. Frequency of chronic comorbid conditions (CCC) by gender.

	Women		Men		All	
Categories	$n = 3573$	%	$n = 4384$	%	$N = 7957$	%
Hypertension	1393	38.99	1758	40.10	3151	39.60
(COPD), emphysema, chronic bronchitis* [a]	1221	34.17	1594	36.36	2815	35.38
Other respiratory diseases***	823	23.03	1202	27.42	2025	25.45
Sleep disorders***	598	16.74	1322	30.16	1920	24.13
Asthma***	988	27.65	732	16.70	1720	21.62
Ischemic heart disease***	544	15.23	1099	25.07	1643	20.65
Allergy***	678	18.98	501	11.43	1179	14.82
Diabetes***	426	11.92	690	15.74	1116	14.03
Other psychiatric and behavioral diseases***	335	9.38	539	12.29	874	10.98
Esophagus, stomach, and duodenum diseases***	442	12.37	410	9.35	852	10.71
Obesity	392	10.97	451	10.29	843	10.59
Heart failure**	322	9.01	475	10.83	797	10.02
Peripheral neuropathy	379	10.61	410	9.35	789	9.92
Dorsopathies	373	10.44	402	9.17	775	9.74
Other musculoskeletal and joint diseases*	335	9.38	354	8.07	689	8.66
Ear, nose, throat diseases***	319	8.93	287	6.55	606	7.62
Other metabolic diseases	259	7.25	313	7.14	572	7.19
Dyslipidemia	248	6.94	322	7.34	570	7.16
Osteoarthritis and other degenerative joint diseases	258	7.22	274	6.25	532	6.69
Inflammatory arthropathies	226	6.33	293	6.68	519	6.52
Neurotic, stress-related and somatoform diseases***	274	7.67	243	5.54	517	6.50
Depression and mood diseases***	282	7.89	197	4.49	479	6.02
Thyroid diseases***	283	7.92	193	4.40	476	5.98
Chronic infectious diseases	195	5.46	273	6.23	468	5.88
Blood and blood forming organ diseases	206	5.77	217	4.95	423	5.32
Anemia	194	5.43	212	4.84	406	5.10
Cerebrovascular disease	176	4.93	229	5.22	405	5.09
Venous and lymphatic diseases***	222	6.21	174	3.97	396	4.98
Other cardiovascular diseases*	150	4.20	237	5.41	387	4.86
Colitis and related diseases	172	4.81	211	4.81	383	4.81
Peripheral vascular disease**	126	3.53	225	5.13	351	4.41
Atrial fibrillation**	125	3.50	208	4.74	333	4.18
Osteoporosis***	195	5.46	89	2.03	284	3.57
Cataract and other lens diseases	103	2.88	119	2.71	222	2.79
Chronic pancreas, biliary tract and gallbladder diseases**	122	3.41	100	2.28	222	2.79
Deafness, hearing impairment	92	2.57	106	2.42	198	2.49
Other genitourinary diseases**	111	3.11	87	1.98	198	2.49
Other neurological diseases	85	2.38	100	2.28	185	2.32
Chronic kidney diseases	74	2.07	94	2.14	168	2.11
Chronic ulcer of the skin	67	1.88	90	2.05	157	1.97
Cardiac valve diseases	76	2.13	74	1.69	150	1.89
Autoimmune diseases	73	2.04	75	1.71	148	1.86
Dementia	54	1.51	71	1.62	125	1.57
Migraine and facial pain syndromes***	77	2.16	37	0.84	114	1.43
Bradycardias and conduction diseases*	37	1.04	74	1.69	111	1.39
Prostate diseases***	1	0.03	89	2.03	90	1.13
Glaucoma	36	1.01	44	1.00	80	1.01
Parkinson and parkinsonism	28	0.78	45	1.03	73	0.92
Chronic liver diseases	26	0.73	40	0.91	66	0.83
Other eye diseases	34	0.95	32	0.73	66	0.83
Epilepsy	22	0.62	36	0.82	58	0.73

Table 2 continued

Categories	Women		Men		All	
	$n = 3573$	%	$n = 4384$	%	$N = 7957$	%
Other digestive diseases	27	0.76	31	0.71	58	0.73
Hermatological neoplasms	19	0.53	38	0.87	57	0.72
Inflammatory bowel diseases	22	0.62	24	0.55	46	0.58
Other skin diseases	26	0.73	20	0.46	46	0.58
Solid neoplasms	14	0.39	12	0.27	26	0.33
Multiple sclerosis	15	0.42	10	0.23	25	0.31
Blindness, visual impairment	6	0.17	9	0.21	15	0.19
Schizophrenia and delusional diseases	5	0.14	5	0.11	10	0.13
Chromosomal abnormalities	0	0	0	0	0	0

Categories are listed in a descending order based on the frequency of each comorbidity in all patients.
*Gender difference significant at $p < 0.05$, **<0.01, ***<0.001 according to χ^2 tests.
[a](COPD), emphysema, chronic bronchitis category excludes COPD (J44) diagnoses.

women due to higher weight points assigned to cardiovascular comorbidities. Although we could not confirm mortality outcomes in our study, previous studies have shown that male COPD patients indeed had higher mortality rates than female COPD patients[12,29]. Men also had more sleep disorders than women did. Considering that poor sleep quality is detrimental to heart health[30], our study corroborated this link between sleep disorders and cardiovascular diseases in our male patients.

Another important aspect of gender-specific comorbidity was linked to quality of life. Depression and anxiety are some of the most significant predictors of quality of life and health status, even more so than spirometry values in COPD patients[31]. The current study demonstrated, despite having lower Elixhauser-vW index scores than men, women more frequently had chronic diseases that affect mental health, which are known to lower the quality of life[12]. The Elixhauser-vW weight algorithm gives the relative importance of each of the comorbidities as they relate to short-term mortality outcomes[21]. However, with patients reaching old age with multiple comorbid conditions, the quality of life indices or algorithms based on chronic comorbid conditions may be equally important in providing optimal care. To create such an algorithm, investigators must consider gender differences and proactively seek to examine comorbidities that are associated with the health-related quality of life.

Although gender-specific comorbidities belong to discrete categories of diseases, some of them have systemic inflammation as a common denominator. COPD is often accompanied by other inflammatory or inflammation-linked diseases such as skeletal muscular disorder, osteoporosis, obesity, diabetes, cardiovascular diseases, and clinical anxiety and depression[14,32]. Indeed our patient sample displayed a high prevalence of cardiovascular diseases, other musculoskeletal and joint diseases, depression, and diabetes. Concerning the coexistence of this observed disease-clustering, some investigators propose that COPD is at the center of the inflammatory process, while others claim that COPD is one of a multitude of possible manifestations of a chronic systemic inflammation[33,34]. Despite the uncertain mechanism of the relationship, reduction in lung function is a risk factor for arrhythmias, acute coronary events, and cardiovascular disease mortality regardless of smoking status among COPD patients[14]. Furthermore, COPD and the common comorbidities such as cardiovascular diseases, skeletal muscle dysfunction, and osteoporosis contribute to a significantly reduced quality of life. Further advancements in research and the treatment of COPD and its comorbidities are crucial to decipher the relations between COPD and its comorbidities.

With regard to the age-specific comorbidities, older patient groups had more comorbidities than the younger groups. However, the 30s, 40s, and 50s groups also displayed a large number of various comorbidities. It has been suggested that COPD accelerates the aging process[35]. The current study seems to supports this hypothesis, as our findings highlight a multitude of chronic conditions in our younger age groups normally common among older patients. For instance, one in four of our patients in the 40s group had other muscular–skeletal and joint diseases. Moreover, the 10-year COPD index period analyses further corroborated age-specific comorbidities by demonstrating that different comorbidities accompanied COPD during the 10-year index period depending on the age of the first COPD diagnosis. Overall more diseases were found with a higher frequency rate in the <45 index age group compared to the other two index age groups among the GP patients. The results of the present study suggest that physicians must consider and monitor these comorbidities right from the start in the individuals developing COPD at a younger age, since they may interfere with COPD disease management. In a previous study examining difficulties in discussing and treating COPD, primary care physicians reported that if a patient does not fit the typical clinical picture of COPD, this often leads to a lack of diagnosis or treatment[28]. For instance, mild or moderate symptoms of COPD among younger or middle-aged patients tend to be overlooked by physicians because they do not correspond to the assumed clinical picture of COPD. In recent years, multiple phenotypes of COPD have been discussed[36]. Despite this, the heterogeneous nature of COPD may still not be common knowledge among GPs, possibly leading to delayed detection and treatment of COPD among younger patients suffering from the disease.

Similarly, most COPD comorbidity research studies include patients 40 or 45 years and older, while the younger patients are excluded. This may be in part due to difficulties in the accurate differential diagnosis of asthma and COPD[37,38], and partly because COPD develops slowly and in general becomes apparent in the 40s and 50s[3]. Nevertheless, our small sample of younger patients exhibited different manifestations of COPD when considering its accompanying conditions. They had psychological problems such as depression and anxiety, while older patients had cardiovascular disorders. Although the current study results need to be interpreted with caution due to a small number of younger patients, our findings seem to indicate different clinical phenotypes of COPD among younger patients. Further research focusing on these age groups is warranted to create a detailed classification of the comorbidity in relation to gender, age, and index age at

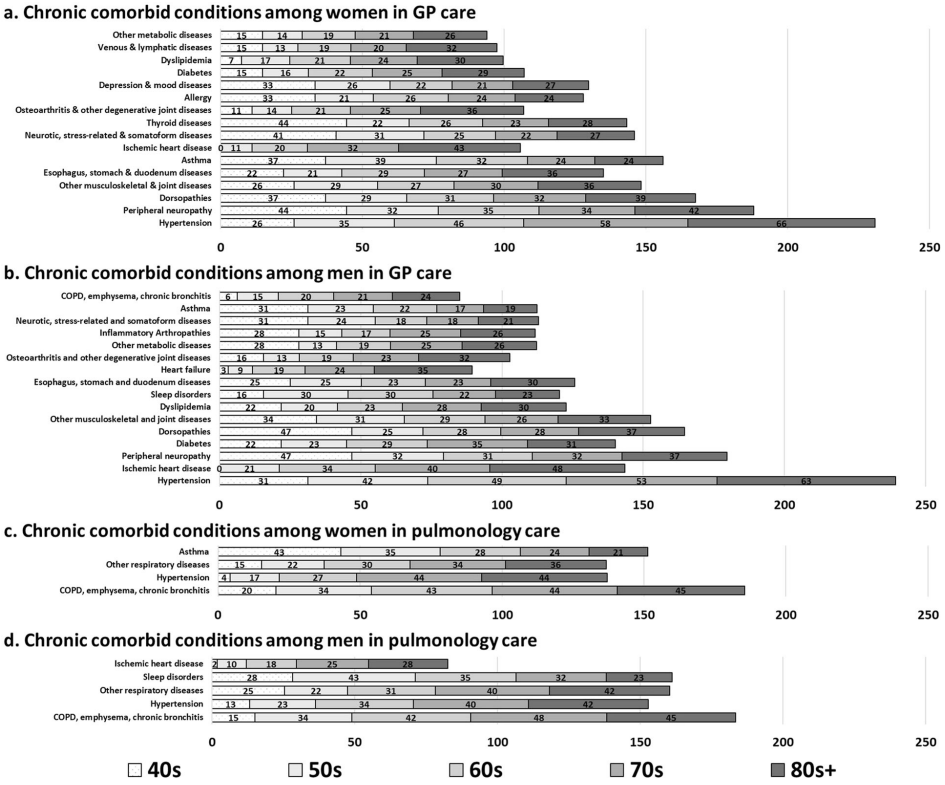

Fig. 4 Chronic comorbid conditions (CCC) with >20% frequency by gender and age group for GP and pulmonology practices. Each segment of bars represents the frequency (%) of the listed comorbid condition for each age group. The conditions are presented in the reverse order of overall frequency by gender and practice.

which COPD symptoms occur. Additionally, the different phenotypes need to be further explored to enhance our understanding of COPD and to guide the treatment of choice for effective care.

The strengths of the current investigation include the use of routine real-world data from GP and pulmonology practices, the detailed examination of gender and age group differences, and the use of an extensive number of chronic comorbid disease categories. Previous studies have shown that COPD patients suffered from significant numbers of comorbidities[8,12,39], and the current study showed gender- and age-specific comorbidities from different practices. Moreover, we examined the comorbidities during the 10-year index period, which provided insights into COPD comorbidity not previously examined. Even one of the most comprehensive data sources such as health insurance claims data normally limit its data handling in the outpatient setting to a maximum of four consecutive years for regulatory reasons[40]. Considering this restriction of the claims data, the comorbidity documented in our study is comprehensive and representative of COPD patients' long-term health status.

The current study has several weaknesses. First, the use of secondary, partly unstructured routine data resulted in the loss of many incomplete patients' data. Due to the use of secondary data, the ICD code documentation could not be verified for its completeness and accuracy because examination of an individual routine of documentation in practice was not possible. Second, our study did not include a comparison group. Gender- and age-matched control group could have allowed comorbidity comparisons between patients with and without COPD. However, the aim of this study was to assess and document comorbid conditions by age and gender among patients with COPD in a real-world setting in primary care. Therefore, we investigated the practice-derived routine documentation of COPD and comorbidities for research purposes. Lastly, this study included a relatively small sample size for the younger age groups and thus the interpretation is limited. Similarly, the 10-year index period analysis also had a small sample size. However, 5 years prior and post of the first COPD documentation was deemed an appropriate index period to examine the accompanying medical conditions due to the average progression of COPD. Longitudinal studies with larger sample sizes including longer observation periods and all age groups are warranted.

In conclusion, patients with COPD seeking treatment in primary care settings have a multitude of chronic conditions. Gender- and age-specific comorbid conditions exist and the documented numbers and categories of comorbidities differ depending on the specialty of the medical practice. The lack of awareness of these comorbidities can lead to a treatment delay, low treatment efficacy, and potentially dangerous drug interactions and their side effects. Understanding gender- and age-specific patterns of comorbidity will help to provide the most effective treatment

Table 3. Twenty most frequent comorbidities among GP patients and 10 most frequent comorbidities among pulmonology patients using chronic comorbid conditions (CCC) over the three index periods (5 years before, ±5 years during the index date, and 5 years after).

GP patients comorbidity scores, mean (SD)														
Index age group	Age < 45: $n = 32$				45 ≤ Age < 65: $n = 218$				Age ≥ 65: $n = 182$					
Chronic comorbid conditions	15.13 (8.19)				14.29 (9.09)				16.12 (9.01)					
Elixhauser	5.56 (3.42)				5.96 (4.23)				6.22 (3.84)					
Elixhauser-vW Index	12.81 (10.47)				14.69 (14.13)				15.92 (12.72)					
20 most frequent comorbidities among GP patients (%)														
Disease categories	Total	Before	Index period	After	Disease categories	Total	Before	Index period	After	Disease categories	Total	Before	Index period	After
Dorsopathies	81.3	40.6	31.3	9.4	Hypertension	71.1	18.3	38.5	14.2	Hypertension	81.3	31.9	43.4	6.0
Peripheral neuropathy	78.1	0	31.3	46.9	Peripheral neuropathy	66.5	37.6	23.4	5.5	Peripheral neuropathy	70.9	41.2	24.2	5.5
Neurotic, stress-related & somatoform d.[a]	71.9	25.0	40.6	6.3	Other musculoskeletal & joint d	62.4	27.1	27.1	8.3	Dorsopathies	68.7	43.4	20.3	4.9
Other musculoskeletal & joint d.	68.8	15.6	31.3	21.9	Dorsopathies	61.0	34.9	22.0	4.1	Other musculoskeletal & joint d.	68.7	35.7	28.6	4.4
Esophagus, stomach & duodenum d.	65.6	6.3	50.0	9.4	Esophagus, stomach & duodenum d.	52.8	20.2	26.1	6.4	Osteoarthritis & other degenerative joint d.	62.6	24.7	31.3	6.6
Ear, nose, throat d.	65.6	18.8	37.5	9.4	Neurotic, stress-related & somatoform d.	49.5	21.6	20.6	7.3	Ischemic heart d.	60.4	29.7	24.2	6.6
Depression & mood d.	62.5	9.4	43.8	9.4	Dyslipidemia	47.7	19.7	22.0	6.0	Esophagus, stomach & duodenum d	56.0	19.2	27.5	9.3
Dyslipidemia	59.4	25.0	21.9	12.5	Ischemic heart disease	46.3	17.0	17.9	11.5	Inflammatory Arthropathies	50.0	27.5	19.2	3.3
Thyroid d.	53.1	9.4	28.1	15.6	Osteoarthritis & other degenerative joint d.	44.0	11.9	22.0	10.1	Dyslipidemia	50.0	25.8	22.0	2.2
Other metabolic d.	53.1	21.9	25.0	6.3	Other metabolic d.	43.6	21.6	15.6	6.4	Other metabolic d.	48.9	26.9	20.3	1.6
Asthma	53.1	18.8	18.8	15.6	Thyroid d.	42.7	11.9	21.6	9.2	Heart failure	44.5	12.6	25.8	6.0
Allergy	50.0	18.8	25.0	6.3	Asthma	40.8	7.8	20.6	12.4	Neurotic, stress-related & somatoform d.	44.5	21.4	18.7	4.4
Hypertension	50.0	9.4	21.9	18.8	Diabetes	40.8	15.1	21.1	4.6	Venous & lymphatic d.	42.9	17.0	18.1	7.7
Inflammatory Arthropathies	46.9	21.9	21.9	3.1	Inflammatory Arthropathies	40.8	22.0	16.1	2.8	Diabetes	39.0	14.3	20.3	4.4
Anemia	46.9	25.0	15.6	6.3	Allergy	39.4	13.8	17.4	8.3	Depression & mood d.	39.0	14.3	17.0	7.7
Blood & blood forming organ d.	43.8	9.4	12.5	21.9	Ear, nose, throat d.	38.1	10.6	18.8	8.7	Colitis & related d.	38.5	13.7	14.8	9.9
Osteoarthritis & other degenerative joint d.	43.8	6.3	15.6	21.9	Blood & blood forming organ d.	37.6	5.0	14.2	18.3	Allergy	37.4	12.1	22.5	2.7
Diabetes	40.6	12.5	18.8	9.4	Colitis & related d.	36.2	10.1	15.6	10.6	Cerebrovascular disease	36.3	11.5	16.5	8.2
Colitis & related d.	37.5	6.3	12.5	18.8	Depression & mood d.	35.8	12.4	17.0	6.4	Thyroid d.	36.3	10.4	22.5	3.3
Venous & lymphatic d.	34.4	3.1	12.5	18.8	Venous & lymphatic d.	35.3	9.6	16.5	9.2	Cataract & other lens d.	36.3	6.0	22.0	8.2

Table 3 continued

Pulmonology patients comorbidity scores, mean (SD)															
Index age group	Age < 45: $n = 49$				45 ≤ Age < 65: $n = 260$				Age ≥ 65: $n = 239$						
Pulmonology patients comorbidity scores, mean (SD)															
Index age group	Age < 45: $n = 49$				45 ≤ Age < 65: $n = 260$				Age ≥ 65: $n = 239$						
Chronic comorbid conditions	3.37 (1.40)				3.18 (1.73)				3.03 (1.53)						
Elixhauser	1.55 (.82)				1.67 (1.14)				1.81 (1.08)						
Elixhauser-vW Index **	3.24 (3.43)				3.68 (3.01)				4.60 (3.4)						
10 most frequent comorbidities among pulmonology patients, %															
Disease categories	Total	Before	Index period	After	Disease categories	Total	Before	Index period	After	Disease categories	Total	Before	Index period	After	Disease categories
Asthma	51.0	30.6	16.3	4.1	(COPD), emphysema, chronic bronchitis	60.8	26.2	28.5	6.2	(COPD), emphysema, chronic bronchitis	61.5	37.2	21.3	2.9	
(COPD), emphysema, chronic bronchitis [b]	49.0	26.5	14.3	8.2	Sleep disorders	36.2	11.5	13.5	11.2	Hypertension	44.4	4.6	22.6	17.2	
Allergy	38.8	20.4	10.2	8.2	Other respiratory d.	33.5	9.2	8.1	16.2	Other respiratory d.	38.1	11.7	14.6	11.7	
Sleep disorders	32.7	10.2	10.2	12.2	Hypertension	32.7	0.8	15.4	16.5	Sleep disorders	27.2	11.3	10.5	5.4	
Other respiratory d.	30.6	22.4	4.10	4.1	Asthma	31.2	21.2	6.9	3.1	Asthma	26.0	18.0	5.9	2.1	
Other psychiatric & behavioral d.	24.5	2.0	14.3	8.2	Allergy	17.0	7.7	5	4.2	Ischemic heart disease	21.8	2.5	7.9	11.3	
Obesity	22.5	0	4.1	18.4	Obesity	15.0	1.2	5	8.8	Allergy	10.0	7.5	2.1	0.4	
Hypertension	20.4	0	6.1	14.3	Other psychiatric & behavioral d	13.1	1.5	9.2	2.3	Diabetes	10.0	0	4.2	5.9	
Chronic infectious d.	12.2	0	4.1	8.2	Ischemic heart disease	12.3	0.8	2.7	8.8	Obesity	7.5	1.7	3.8	2.1	
Esophagus, stomach, & duodenum d.	8.2	2.0	2.0	4.1	Diabetes	8.1	1.2	1.2	5.8	Other psychiatric & behavioral d.	7.1	0.4	5.4	1.3	

**Three index age group difference significant at $p < 0.01$ according to ANOVA.
[a]d.= diseases.
[b](COPD), emphysema, chronic bronchitis—frequency is based on the data excluding J44 diagnosis.

options for all COPD patients. With no cure for COPD presently available, early identification of comorbid conditions and selecting the best treatment options will reduce disease burdens and improve COPD patients' overall health and quality of life. Physicians treating patients with COPD should be cognizant of these comorbidities, their early onset, and actively assess these conditions. Future studies of COPD comorbidities should include young adult patients and use gender- and age-stratification to make accurate evaluations and implement effective disease and symptom management.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

All authors contributed to the conception and design of the study. S.-J.K.-D., T.S., A.K., and H.L. analyzed and interpreted data. S.-J.K.-D. wrote the initial draft and all authors critically revised the paper. All authors read and approved the final manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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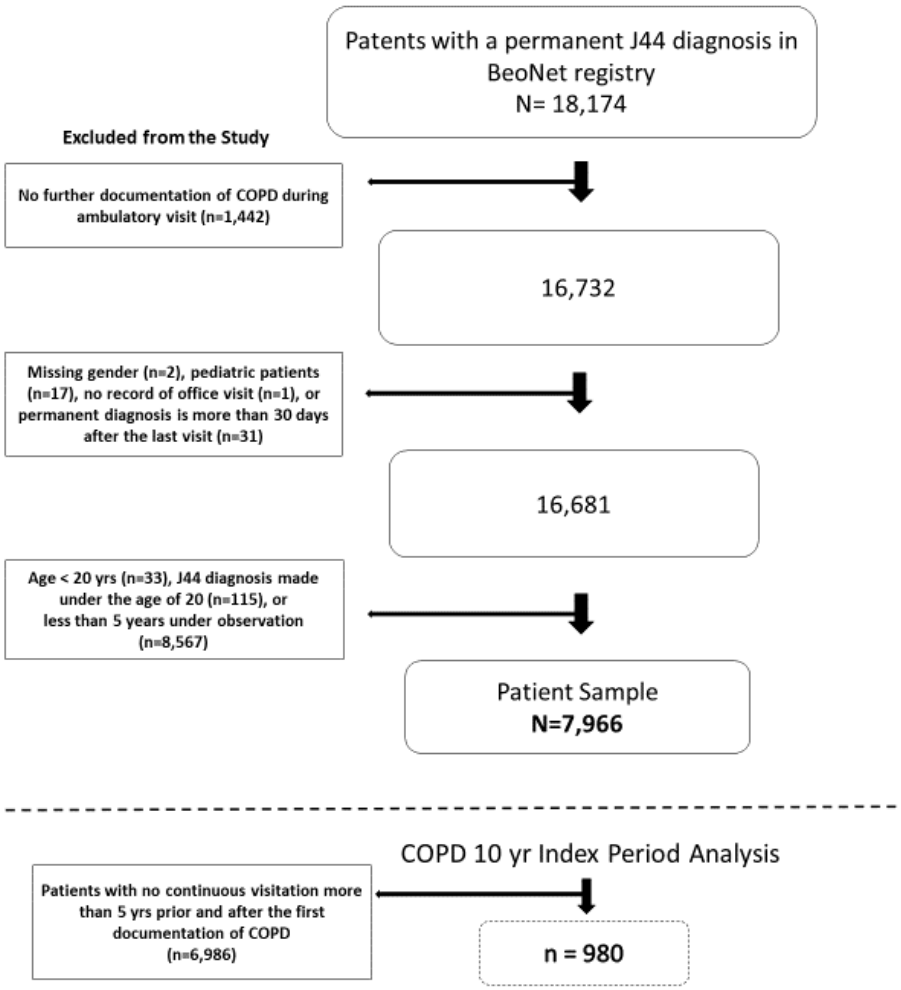
Additional File 1. Supplementary figure and tables

Supplementary Figure 1. Data Flowchart. BeoNet registry patient data for the main and index period analyses



Supplementary Table 1. Post-hoc Bonferroni test p values for the age group comparison

		P values		
Age Group	**Comparison Age Group**	**CCC**	**Elixhauser**	**Elixhauser-vW index**
30	40	1.000	1.000	1.000
	50	1.000	1.000	1.000
	60	1.000	0.831	1.000
	70	1.000	0.044	0.126
	80	0.047	0.001	0.000
40	30	1.000	1.000	1.000
	50	1.000	0.899	1.000
	60	0.141	0.000	0.005
	70	0.007	0.000	0.000
	80	0.000	0.000	0.000
50	30	1.000	1.000	1.000
	40	1.000	0.899	1.000
	60	0.256	0.001	0.000
	70	0.001	0.000	0.000
	80	0.000	0.000	0.000
60	30	1.000	0.831	1.000
	40	0.141	0.000	0.005
	50	0.256	0.001	0.000
	70	0.933	0.000	0.001
	80	0.000	0.000	0.000
70	30	1.000	0.044	0.126
	40	0.007	0.000	0.000
	50	0.001	0.000	0.000
	60	0.933	0.000	0.001
	80	0.000	0.000	0.000
80	30	0.047	0.001	0.000
	40	0.000	0.000	0.000
	50	0.000	0.000	0.000
	60	0.000	0.000	0.000
	70	0.000	0.000	0.000

Supplementary Table 2. Elixhauser comorbid conditions by gender and combined

		Women		**Men**		**All**	
	vW weight	n = 3573	%	n =4384	%	n = 7957	%
Chronic pulmonary disease (with COPD)	3	3,573	(100.0)	4,384	(100.0)	7,957	(100.0)
Chronic pulmonary disease (no COPD)	3	1,987 ***	(55.6)	2,233	(50.9)	4,220	(53.0)
Hypertension	0	1,393	(39.0)	1,758	(40.1)	3,151	(39.6)
Diabetes, uncomplicated	0	396	(11.1)	635 ***	(14.5)	1,031	(13.0)
Solid tumor without metastasis	4	359	(10.0)	643 ***	(14.7)	1,002	(12.6)
Obesity	-4	392	(11.0)	451	(10.3)	843	(10.6)
Cardiac arrhythmias	5	322	(9.0)	489 **	(11.2)	811	(10.2)
Congestive heart failure	7	282	(7.9)	409 *	(9.3)	691	(8.7)
Depression	-3	291 ***	(8.1)	213	(4.9)	504	(6.3)
Peripheral vascular disorders	2	164	(4.6)	304 ***	(6.9)	468	(5.9)
Pulmonary circulation Disorders	4	154	(4.3)	202	(4.6)	356	(4.5)
Liver disease	11	144	(4.0)	201	(4.6)	345	(4.3)
Rheumatoid arthritis/collagen vascular diseases	0	163 *	(4.6)	160	(3.6)	323	(4.1)
Renal failure	5	119	(3.3)	140	(3.2)	259	(3.3)
Hypothyroidism	0	163 ***	(4.6)	94	(2.1)	257	(3.2)
Diabetes, complicated	0	90	(2.5)	153 *	(3.5)	243	(3.1)
Fluid and electrolyte disorders	5	101	(2.8)	111	(2.5)	212	(2.7)
Deficiency anemia	-2	109 *	(3.1)	100	(2.3)	209	(2.6)
Coagulopathy	3	73	(2.0)	107	(2.4)	180	(2.3)
Other neurological disorders	6	67	(1.9)	106	(2.4)	173	(2.2)
Valvular disease	-1	74	(2.1)	70	(1.6)	144	(1.8)
Weight loss	6	61	(1.7)	67	(1.5)	128	(1.6)
Peptic ulcer disease excluding bleeding	0	49	(1.4)	63	(1.4)	112	(1.4)
Alcohol abuse	0	29	(0.8)	69 **	(1.6)	98	(1.2)
Metastatic Cancer	12	29	(0.8)	57 *	(1.3)	86	(1.1)
Blood loss anemia	-2	24	(0.7)	22	(0.5)	46	(0.6)
Lymphoma	9	13	(0.4)	23	(0.5)	36	(0.5)
Paralysis	7	16	(0.4)	17	(0.4)	33	(0.4)
Psychoses	0	14	(0.4)	13	(0.3)	27	(0.3)
Drug abuse	-7	8	(0.2)	15	(0.3)	23	(0.3)
AIDS/HIV	0	1	(0.0)	2	(0.0)	3	(0.0)

Elixhauser categories are listed in a descending order based on comorbidity frequency of all patients excluding the 20s group.

* Gender difference significant at p < .05; ** p<.01; *** p<.001 according to Chi-squared tests.

Supplementary Table 3. Chronic comorbid conditions (CCC), Elixhauser, and Elixhauser-van Walraven index comorbidity by gender and age for practice types (GPs and Pulmonologists)

		Chronic comorbid conditions (CCC) †§																				
		GP											**Pulmonology**									
		Women						**Men**					**Women**						**Men**			
Age Group		n	M	(SD)	Mdn	Range		n	M	(SD)	Mdn	Range	n	M	(SD)	Mdn	Range		n	M	(SD)	Mdn	Range
30s [a]		7	7.71	5.56	7	0-19		6	9.83	7.41	8.5	1-20	27	1.85	1.20	2	0-5		34	2.06	1.30	2	0-5
40s		27	5.96	4.78	5	0-16		32	6.44	5.87	5	0-19	118	2.06	1.34	2	0-7		106	1.97	1.40	2	0-7
50s		136	5.84	6.57	3	0-29		151	5.90	6.20	3	0-32	357	2.18	1.46	2	0-9		433	2.47	1.53	2	0-8
60s		285	7.01	7.95	3	0-35		312	6.78	7.46	3	0-31	708	2.45	1.62	2	0-8		843	2.60	1.52	2	0-9
70s		271	7.49	8.36	3	0-32		356	7.80	8.57	4	0-36	777	2.69	1.57	3	0-9		1074	2.87	1.65	3	0-9
80+		294	10.26	10.25	6	0-42		315	9.51	9.53	6	0-37	566	2.57	1.44	2	0-7		722	2.68	1.59	3	0-9
Total		1,020	7.90	8.68				1,172	7.72	8.31			2,553	2.49	1.54				3,212	2.66	1.59		
		Elixhauser †§																				
30s [a]		7	2.86	2.48	3	1-8		6	3.67	3.39	3.5	0-8	27	.96	.90	1	0-4		34	.91	.71	1	0-3
40s		27	2.33	1.78	2	0-6		32	2.72	2.82	2	0-10	118	.90	.79	1	0-4		106	.87	.86	1	0-4
50s		136	2.57	2.74	2	0-12		151	2.63	2.78	2	0-13	357	1.04	.83	1	0-5		433	1.19	1.03	1	0-5
60s		285	3.09	3.41	2	0-16		312	3.17	3.48	2	0-15	708	1.32	.99	1	0-4		843	1.40	1.05	1	0-6
70s		271	3.48	3.70	2	0-18		356	3.66	3.81	2	0-19	777	1.63	1.08	1	0-6		1074	1.67	1.16	1	0-7
80+		294	4.15	4.08	3	0-22		315	4.12	4.03	3	0-18	566	1.61	1.10	2	0-7		722	1.70	1.17	2	0-6
Total		1,020	3.44	3.67				1,172	3.49	3.67			2,553	1.41	1.04				3,212	1.50	1.13		
		Elixhauser-van Walraven index *†§																				
30s [a]		7	5.29	5.41	3	0-15		6	13.00	9.06	14.5	3-27	27	2.11	1.69	3	-1-3		34	2.97	1.85	3	-1-10
40s		27	3.56	4.59	3	-4-16		32	7.66	8.50	3	-7-36	118	2.88	2.17	3	-4-10		106	2.86	2.09	3	-1-11
50s		136	5.80	7.65	3	-4-36		151	6.26	7.42	3	-9-32	357	2.83	2.17	3	-4-19		433	3.23	2.73	3	-4-26
60s		285	7.66	9.76	3	-4-60		312	9.47	10.72	3	-4-53	708	3.35	2.84	3	-5-19		843	3.77	2.88	3	-4-19
70s		271	9.02	9.67	3	-1-46		356	10.95	11.51	7	-1-55	777	3.87	3.09	3	-4-19		1074	4.55	3.68	3	-4-25
80+		294	11.27	11.19	7	-4-67		315	12.08	12.28	7	-1-61	566	4.33	3.28	3	-1-19		722	5.03	3.75	3	-1-24
Total		1,020	8.69	10.00				1,172	10.18	11.13			2,553	3.62	2.95				3,212	4.20	3.39	3	

[a] The 30s group was excluded from GPs vs. Pulmonologists analyses due to the small sample size but the raw data are presented here.

* Gender group difference significant at p < .001; †Age group difference significant at *p* < .001; § Practice difference significant at *p* < .001 based on ANOVA.

Supplementary Table 4. Post-hoc Bonferroni test p values for the age group comparison by practice types

		P values					
		GP Patients			Pulmonology Patients		
Age Group	Comparison Age Group	CCC	Elixhauser	Elixhauser-vW Index	CCC	Elixhauser	Elixhauser-vW Index
40	50	1.000	1.000	1.000	0.060	0.031	1.000
	60	1.000	1.000	0.481	0.000	0.000	0.018
	70	1.000	0.355	0.024	0.000	0.000	0.000
	80	0.014	0.013	0.000	0.000	0.000	0.000
50	40	1.000	1.000	1.000	0.060	0.031	1.000
	60	0.924	0.397	0.007	0.051	0.000	0.001
	70	0.027	0.001	0.000	0.000	0.000	0.000
	80	0.000	0.000	0.000	0.000	0.000	0.000
60	40	1.000	1.000	0.481	0.000	0.000	0.018
	50	0.924	0.397	0.007	0.051	0.000	0.001
	70	1.000	0.316	0.118	0.000	0.000	0.000
	80	0.000	0.000	0.000	0.879	0.000	0.000
70	40	1.000	0.355	0.024	0.000	0.000	0.000
	50	0.027	0.001	0.000	0.000	0.000	0.000
	60	1.000	0.316	0.118	0.000	0.000	0.000
	80	0.000	0.072	0.084	0.043	1.000	0.001
80	40	0.014	0.013	0.000	0.000	0.000	0.000
	50	0.000	0.000	0.000	0.000	0.000	0.000
	60	0.000	0.000	0.000	0.879	0.000	0.000
	70	0.000	0.072	0.084	0.043	1.000	0.001

The 30s group was excluded from the analysis due to the small sample size.

Supplementary Table 5. Gender and age stratified comorbidity per practice type.

General Practitioner												
	Women											
Chronic Comorbid Disease Categories	**All = 1,013**		**40s = 27**		**50s = 136**		**60s = 285**		**70s = 271**		**80s+ = 294**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Hypertension	536	52.9	7	25.9	48	35.3	130	45.6	157	57.9	194	66.0
Peripheral neuropathy	372	36.7	12	44.4	44	32.4	101	35.4	92	33.9	123	41.8
Dorsopathies	338	33.4	10	37.0	39	28.7	87	30.5	88	32.5	114	38.8
Other musculoskeletal & joint diseases	311	30.7	7	25.9	40	29.4	77	27.0	80	29.5	107	36.4
Esophagus, stomach & duodenum diseases	296	29.2	6	22.2	28	20.6	83	29.1	74	27.3	105	35.7
Asthma	290	28.6	10	37.0	53	39.0	92	32.3	64	23.6	71	24.1
Ischemic heart disease	284	28.0	0	0.0	15	11.0	56	19.6	87	32.1	126	42.9
Neurotic, stress-related & somatoform diseases	264	26.1	11	40.7	42	30.9	72	25.3	59	21.8	80	27.2
Thyroid diseases	260	25.7	12	44.4	30	22.1	74	26.0	63	23.2	81	27.6
Osteoarthritis & other degenerative joint diseases	255	25.2	3	11.1	19	14.0	59	20.7	67	24.7	107	36.4
Allergy	247	24.4	9	33.3	28	20.6	75	26.3	64	23.6	71	24.1
Depression & mood diseases	244	24.1	9	33.3	36	26.5	62	21.8	58	21.4	79	26.9
Diabetes	242	23.9	4	14.8	22	16.2	64	22.5	67	24.7	85	28.9
Dyslipidemia	239	23.6	2	7.4	23	16.9	61	21.4	64	23.6	89	30.3
Venous & lymphatic diseases	221	21.8	4	14.8	17	12.5	53	18.6	53	19.6	94	32.0
Other metabolic diseases	208	20.5	4	14.8	19	14.0	53	18.6	56	20.7	76	25.9
Heart failure	202	19.9	1	3.7	9	6.6	34	11.9	59	21.8	99	33.7
Inflammatory Arthropathies	196	19.3	3	11.1	14	10.3	49	17.2	53	19.6	77	26.2
Sleep disorders	192	19.0	4	14.8	28	20.6	65	22.8	50	18.5	45	15.3
Anemia	191	18.9	4	14.8	21	15.4	50	17.5	48	17.7	68	23.1
Ear, nose, throat diseases	189	18.7	7	25.9	31	22.8	44	15.4	49	18.1	58	19.7
(COPD), emphysema, chronic bronchitis [a]	172	17.0	2	7.4	20	14.7	55	19.3	51	18.8	44	15.0
Colitis & related diseases	169	16.7	3	11.1	17	12.5	38	13.3	39	14.4	72	24.5
Cerebrovascular diseases	153	15.1	0	0.0	6	4.4	27	9.5	36	13.3	84	28.6
Blood & blood forming organ diseases	147	14.5	2	7.4	17	12.5	45	15.8	33	12.2	50	17.0
Other cardiovascular diseases	121	11.9	2	7.4	14	10.3	26	9.1	29	10.7	50	17.0
Chronic pancreas, biliary tract & gallbladder diseases	121	11.9	2	7.4	11	8.1	33	11.6	22	8.1	53	18.0
Peripheral vascular diseases	114	11.3	0	0.0	3	2.2	24	8.4	34	12.5	53	18.0
Osteoporosis	112	11.1	1	3.7	2	1.5	19	6.7	30	11.1	60	20.4

Other genitourinary diseases	111	11.0		0	0.0	6	4.4	28	9.8	25	9.2	52	17.7
Cataract and other lens diseases	98	9.7		0	0.0	1	0.7	12	4.2	30	11.1	55	18.7
Deafness, hearing impairment	92	9.1		2	7.4	6	4.4	16	5.6	24	8.9	44	15.0
Atrial Fibrillation	79	7.8		1	3.7	1	0.7	8	2.8	19	7.0	50	17.0
Obesity	77	7.6		3	11.1	11	8.1	26	9.1	25	9.2	12	4.1
Other neurological diseases	76	7.5		3	11.1	3	2.2	20	7.0	16	5.9	34	11.6
Migraine and facial pain syndromes	71	7.0		1	3.7	18	13.2	20	7.0	15	5.5	17	5.8
Chronic ulcer of the skin	67	6.6		0	0.0	4	2.9	10	3.5	9	3.3	44	15.0
Cardiac valve diseases	59	5.8		0	0.0	3	2.2	9	3.2	16	5.9	31	10.5
Dementia	53	5.2		0	0.0	0	0.0	2	0.7	8	3.0	43	14.6
Chronic kidney diseases	57	5.6		0	0.0	3	2.2	11	3.9	14	5.2	29	9.9
Other psychiatric and behavioral diseases	68	6.7		2	7.4	9	6.6	22	7.7	16	5.9	19	6.5
Other respiratory diseases	48	4.7		2	7.4	9	6.6	14	4.9	8	3.0	15	5.1
Chronic infectious diseases	46	4.5		2	7.4	4	2.9	15	5.3	10	3.7	15	5.1
Epilepsy	15	1.5		2	7.4	1	0.7	1	0.4	4	1.5	7	2.4
Autoimmune diseases	53	5.2		1	3.7	8	5.9	17	6.0	7	2.6	20	6.8
Other eye diseases	33	3.3		0	0.0	2	1.5	9	3.2	6	2.2	16	5.4
Other digestive diseases	27	2.7		0	0.0	2	1.5	3	1.1	6	2.2	16	5.4
Bradycardias and conduction diseases	25	2.5		0	0.0	2	1.5	2	0.7	5	1.8	16	5.4
Parkinson and parkinsonism	24	2.4		0	0.0	0	0.0	2	0.7	10	3.7	12	4.1
Glaucoma	22	2.2		0	0.0	0	0.0	3	1.1	7	2.6	12	4.1
Other skin diseases	25	2.5		1	3.7	0	0.0	9	3.2	5	1.8	10	3.4
Chronic liver diseases	25	2.5		0	0.0	1	0.7	10	3.5	4	1.5	10	3.4
Solid neoplasms	14	1.4		0	0.0	0	0.0	5	1.8	1	0.4	8	2.7
Hermatological neoplasms	13	1.3		0	0.0	0	0.0	3	1.1	7	2.6	3	1.0
Inflammatory bowel diseases	17	1.7		0	0.0	2	1.5	6	2.1	4	1.5	5	1.7
Multiple sclerosis	6	0.6		0	0.0	2	1.5	3	1.1	0	0.0	1	0.3
Blindness, visual impairment	6	0.6		0	0.0	0	0.0	1	0.4	1	0.4	4	1.4
Schizophrenia and delusional diseases	5	0.5		0	0.0	0	0.0	2	0.7	2	0.7	1	0.3
Prostate diseases	1	0.1		0	0.0	0	0.0	0	0.0	0	0.0	1	0.3
Chromosomal abnormalities	0	0											
	Men												
	All = 1,166			**40s = 32**		**50s = 151**		**60s = 312**		**70s = 356**		**80s+ = 315**	
Hypertension	616	52.8		10	31.3	64	42.4	153	49.0	190	53.4	199	63.2

Ischemic heart disease	433	37.1		0	0.0	32	21.2	106	34.0	144	40.4	151	47.9
Peripheral neuropathy	392	33.6		15	46.9	49	32.5	98	31.4	113	31.7	117	37.1
Diabetes	355	30.4		7	21.9	35	23.2	89	28.5	126	35.4	98	31.1
Dorsopathies	355	30.4		15	46.9	38	25.2	86	27.6	98	27.5	118	37.5
Other musculoskeletal and joint diseases	342	29.3		11	34.4	47	31.1	89	28.5	92	25.8	103	32.7
Dyslipidemia	303	26.0		7	21.9	30	19.9	72	23.1	99	27.8	95	30.2
Sleep disorders	294	25.2		5	15.6	45	29.8	94	30.1	79	22.2	71	22.5
Esophagus, stomach and duodenum diseases	293	25.1		8	25.0	38	25.2	71	22.8	82	23.0	94	29.8
Heart failure	268	23.0		1	3.1	13	8.6	58	18.6	87	24.4	109	34.6
Osteoarthritis and other degenerative joint diseases	268	23.0		5	15.6	19	12.6	60	19.2	82	23.0	102	32.4
Other metabolic diseases	262	22.5		9	28.1	20	13.2	60	19.2	90	25.3	83	26.3
Inflammatory Arthropathies	257	22.0		9	28.1	23	15.2	53	17.0	89	25.0	83	26.3
Neurotic, stress-related and somatoform diseases	235	20.2		10	31.3	36	23.8	57	18.3	65	18.3	67	21.3
Asthma	234	20.1		10	31.3	35	23.2	70	22.4	59	16.6	60	19.0
(COPD), emphysema, chronic bronchitis	234	20.1		2	6.3	22	14.6	61	19.6	74	20.8	75	23.8
Colitis and related diseases	210	18.0		6	18.8	19	12.6	51	16.3	63	17.7	71	22.5
Anemia	207	17.8		7	21.9	19	12.6	42	13.5	67	18.8	72	22.9
Cerebrovascular disease	202	17.3		1	3.1	12	7.9	32	10.3	76	21.3	81	25.7
Allergy	190	16.3		7	21.9	26	17.2	54	17.3	50	14.0	53	16.8
Thyroid diseases	185	15.9		8	25.0	24	15.9	48	15.4	51	14.3	54	17.1
Peripheral vascular disease	182	15.6		2	6.3	10	6.6	38	12.2	78	21.9	54	17.1
Venous and lymphatic diseases	172	14.8		1	3.1	12	7.9	40	12.8	50	14.0	69	21.9
Other cardiovascular diseases	168	14.4		2	6.3	12	7.9	30	9.6	68	19.1	56	17.8
Ear, nose, throat diseases	165	14.2		10	31.3	22	14.6	35	11.2	44	12.4	54	17.1
Other psychiatric and behavioral diseases	164	14.1		3	9.4	23	15.2	53	17.0	52	14.6	33	10.5
Depression and mood diseases	161	13.8		7	21.9	26	17.2	38	12.2	43	12.1	47	14.9
Blood and blood forming organ diseases	160	13.7		3	9.4	18	11.9	36	11.5	47	13.2	56	17.8
Atrial Fibrillation	129	11.1		1	3.1	4	2.6	32	10.3	41	11.5	51	16.2
Cataract and other lens diseases	107	9.2		0	0.0	1	0.7	10	3.2	35	9.8	61	19.4
Deafness, hearing impairment	103	8.8		1	3.1	3	2.0	24	7.7	25	7.0	50	15.9
Chronic pancreas, biliary tract and gallbladder diseases	98	8.4		5	15.6	10	6.6	18	5.8	27	7.6	38	12.1
Obesity	95	8.1		4	12.5	12	7.9	27	8.7	31	8.7	21	6.7
Chronic ulcer of the skin	90	7.7		0	0.0	7	4.6	15	4.8	29	8.1	39	12.4
Prostate diseases	89	7.6		1	3.1	5	3.3	10	3.2	31	8.7	42	13.3

Other genitourinary diseases	86	7.4		3	9.4	4	2.6	15	4.8	31	8.7	33	10.5
Other neurological diseases	85	7.3		1	3.1	6	4.0	14	4.5	25	7.0	39	12.4
Other respiratory diseases	83	7.1		0	0.0	9	6.0	19	6.1	25	7.0	30	9.5
Dementia	67	5.7		0	0.0	1	0.7	3	1.0	16	4.5	47	14.9
Chronic infectious diseases	64	5.5		0	0.0	7	4.6	19	6.1	18	5.1	20	6.3
Chronic kidney diseases	64	5.5		2	6.3	2	1.3	12	3.8	21	5.9	27	8.6
Autoimmune diseases	62	5.3		0	0.0	5	3.3	17	5.4	21	5.9	19	6.0
Cardiac valve diseases	51	4.4		0	0.0	8	5.3	6	1.9	13	3.7	24	7.6
Bradycardias and conduction diseases	46	3.9		0	0.0	1	0.7	8	2.6	18	5.1	19	6.0
Osteoporosis	45	3.9		0	0.0	1	0.7	10	3.2	18	5.1	16	5.1
Chronic liver diseases	36	3.1		1	3.1	9	6.0	15	4.8	9	2.5	2	0.6
Glaucoma	35	3.0		1	3.1	3	2.0	7	2.2	9	2.5	15	4.8
Migraine and facial pain syndromes	34	2.9		1	3.1	7	4.6	12	3.8	8	2.2	6	1.9
Other digestive diseases	31	2.7		1	3.1	1	0.7	8	2.6	8	2.2	13	4.1
Other eye diseases	31	2.7		1	3.1	2	1.3	8	2.6	8	2.2	12	3.8
Parkinson and parkinsonism	27	2.3		0	0.0	1	0.7	1	0.3	12	3.4	13	4.1
Epilepsy	23	2.0		0	0.0	6	4.0	3	1.0	9	2.5	5	1.6
Hermatological neoplasms	23	2.0		2	6.3	2	1.3	4	1.3	8	2.2	7	2.2
Inflammatory bowel diseases	21	1.8		0	0.0	2	1.3	6	1.9	7	2.0	6	1.9
Other skin diseases	20	1.7		0	0.0	0	0.0	9	2.9	6	1.7	5	1.6
Solid neoplasms	10	0.9		0	0.0	0	0.0	1	0.3	4	1.1	5	1.6
Blindness, visual impairment	9	0.8		0	0.0	1	0.7	0	0.0	4	1.1	4	1.3
Multiple sclerosis	9	0.8		0	0.0	1	0.7	6	1.9	1	0.3	1	0.3
Schizophrenia and delusional diseases	4	0.3		0	0.0	1	0.7	1	0.3	0	0.0	2	0.6
Chromosomal abnormalities	0	0											
Pulmonologist													
	Women												
	All = 2,526			**40s = 118**		**50s = 357**		**60s = 708**		**70s = 777**		**80s+ = 566**	
(COPD), emphysema, chronic bronchitis	1,042	41.3		24	20.3	120	33.6	302	42.7	342	44.0	254	44.9
Hypertension	852	33.7		5	4.2	62	17.4	193	27.3	341	43.9	251	44.3
Other respiratory diseases	773	30.6		18	15.3	79	22.1	214	30.2	261	33.6	201	35.5
Asthma	681	27.0		51	43.2	125	35.0	200	28.2	188	24.2	117	20.7
Allergy	420	16.6		44	37.3	92	25.8	129	18.2	100	12.9	55	9.7

Sleep disorders	404	16.0		15	12.7	60	16.8	143	20.2	123	15.8	63	11.1
Obesity	308	12.2		16	13.6	46	12.9	92	13.0	102	13.1	52	9.2
Other psychiatric and behavioral diseases	261	10.3		20	16.9	59	16.5	99	14.0	68	8.8	15	2.7
Ischemic heart disease	260	10.3		0	0.0	9	2.5	41	5.8	107	13.8	103	18.2
Diabetes	182	7.2		1	0.8	13	3.6	31	4.4	81	10.4	56	9.9
Chronic infectious diseases	147	5.8		7	5.9	22	6.2	39	5.5	52	6.7	27	4.8
Esophagus, stomach and duodenum diseases	142	5.6		5	4.2	12	3.4	44	6.2	48	6.2	33	5.8
Ear, nose, throat diseases	127	5.0		8	6.8	18	5.0	35	4.9	38	4.9	28	4.9
Heart failure	120	4.8		2	1.7	4	1.1	20	2.8	45	5.8	49	8.7
Osteoporosis	83	3.3		1	0.8	4	1.1	13	1.8	38	4.9	27	4.8
Blood and blood forming organ diseases	58	2.3		4	3.4	8	2.2	11	1.6	16	2.1	19	3.4
Other metabolic diseases	50	2.0		5	4.2	10	2.8	27	3.8	7	0.9	1	0.2
Atrial Fibrillation	46	1.8		0	0.0	0	0.0	4	0.6	16	2.1	26	4.6
Depression and mood diseases	36	1.4		4	3.4	6	1.7	15	2.1	7	0.9	4	0.7
Dorsopathies	32	1.3		0	0.0	5	1.4	10	1.4	9	1.2	8	1.4
Inflammatory Arthropathies	29	1.1		1	0.8	2	0.6	12	1.7	9	1.2	5	0.9
Other cardiovascular diseases	28	1.1		0	0.0	1	0.3	2	0.3	14	1.8	11	1.9
Cerebrovascular disease	23	0.9		1	0.8	2	0.6	4	0.6	9	1.2	7	1.2
Thyroid diseases	22	0.9		0	0.0	5	1.4	6	0.8	7	0.9	4	0.7
Autoimmune diseases	20	0.8		0	0.0	2	0.6	6	0.8	8	1.0	4	0.7
Other musculoskeletal and joint diseases	18	0.7		0	0.0	3	0.8	6	0.8	9	1.2	0	0.0
Chronic kidney diseases	17	0.7		0	0.0	1	0.3	3	0.4	7	0.9	6	1.1
Cardiac valve diseases	16	0.6		0	0.0	0	0.0	5	0.7	6	0.8	5	0.9
Glaucoma	14	0.6		1	0.8	1	0.3	3	0.4	4	0.5	5	0.9
Peripheral vascular disease	12	0.5		0	0.0	0	0.0	4	0.6	5	0.6	3	0.5
Bradycardias and conduction diseases	10	0.4		0	0.0	0	0.0	2	0.3	3	0.4	5	0.9
Multiple sclerosis	9	0.4		2	1.7	1	0.3	5	0.7	1	0.1	0	0.0
Other neurological diseases	9	0.4		1	0.8	1	0.3	4	0.6	1	0.1	2	0.4
Dyslipidemia	8	0.3		0	0.0	2	0.6	0	0.0	6	0.8	0	0.0
Epilepsy	7	0.3		2	1.7	1	0.3	1	0.1	3	0.4	0	0.0
Hermatological neoplasms	6	0.2		0	0.0	0	0.0	1	0.1	4	0.5	1	0.2
Inflammatory bowel diseases	5	0.2		0	0.0	2	0.6	2	0.3	1	0.1	0	0.0
Neurotic, stress-related and somatoform diseases	5	0.2		2	1.7	1	0.3	2	0.3	0	0.0	0	0.0
Cataract and other lens diseases	5	0.2		0	0.0	0	0.0	0	0.0	3	0.4	2	0.4

Migraine and facial pain syndromes	4	0.2		1	0.8	0	0.0	2	0.3	1	0.1	0	0.0
Parkinson and parkinsonism	4	0.2		0	0.0	0	0.0	1	0.1	1	0.1	2	0.4
Peripheral neuropathy	4	0.2		1	0.8	0	0.0	0	0.0	0	0.0	3	0.5
Colitis and related diseases	2	0.1		0	0.0	1	0.3	0	0.0	0	0.0	1	0.2
Anemia	2	0.1		0	0.0	0	0.0	0	0.0	2	0.3	0	0.0
Osteoarthritis and other degenerative joint diseases	2	0.1		1	0.8	0	0.0	1	0.1	0	0.0	0	0.0
Chronic liver diseases	1	0.0		0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Dementia	1	0.0		0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Other eye diseases	1	0.0		0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Blindness, visual impairment	0	0											
Chromosomal abnormalities	0	0											
Chronic pancreas, biliary tract and gallbladder diseases	0	0											
Chronic ulcer of the skin	0	0											
Deafness, hearing impairment	0	0											
Other digestive diseases	0	0											
Other genitourinary diseases	0	0											
Other skin diseases	0	0											
Prostate diseases	0	0											
Schizophrenia and delusional diseases	0	0											
Solid neoplasms	0	0											
Venous and lymphatic diseases	0	0											
	Men												
	All = 3,178			**40s = 106**		**50s = 433**		**60s = 843**		**70s = 1,074**		**80s+ = 722**	
(COPD), emphysema, chronic bronchitis	1,351	42.5		16	15.1	147	33.9	351	41.6	512	47.7	325	45.0
Hypertension	1,139	35.8		14	13.2	100	23.1	289	34.3	433	40.3	303	42.0
Other respiratory diseases	1,116	35.1		27	25.5	95	21.9	260	30.8	430	40.0	304	42.1
Sleep disorders	1,019	32.1		30	28.3	186	43.0	297	35.2	339	31.6	167	23.1
Ischemic heart disease	665	20.9		2	1.9	44	10.2	148	17.6	271	25.2	200	27.7
Asthma	476	15.0		34	32.1	97	22.4	138	16.4	138	12.8	69	9.6
Other psychiatric and behavioral diseases	367	11.5		15	14.2	94	21.7	123	14.6	109	10.1	26	3.6
Obesity	353	11.1		14	13.2	61	14.1	99	11.7	119	11.1	60	8.3
Diabetes	331	10.4		3	2.8	27	6.2	79	9.4	136	12.7	86	11.9
Allergy	299	9.4		22	20.8	59	13.6	81	9.6	92	8.6	45	6.2
Chronic infectious diseases	208	6.5		4	3.8	26	6.0	48	5.7	82	7.6	48	6.6

Heart failure	205	6.5		2	1.9	10	2.3	39	4.6	85	7.9	69	9.6
Ear, nose, throat diseases	117	3.7		5	4.7	17	3.9	27	3.2	40	3.7	28	3.9
Esophagus, stomach and duodenum diseases	114	3.6		6	5.7	19	4.4	32	3.8	33	3.1	24	3.3
Atrial Fibrillation	78	2.5		0	0.0	5	1.2	13	1.5	24	2.2	36	5.0
Other cardiovascular diseases	69	2.2		0	0.0	5	1.2	13	1.5	34	3.2	17	2.4
Blood and blood forming organ diseases	54	1.7		2	1.9	6	1.4	24	2.8	16	1.5	6	0.8
Other metabolic diseases	48	1.5		4	3.8	10	2.3	15	1.8	11	1.0	8	1.1
Dorsopathies	43	1.4		0	0.0	3	0.7	10	1.2	22	2.0	8	1.1
Peripheral vascular disease	43	1.4		0	0.0	3	0.7	14	1.7	18	1.7	8	1.1
Osteoporosis	43	1.4		1	0.9	5	1.2	12	1.4	14	1.3	11	1.5
Depression and mood diseases	35	1.1		3	2.8	16	3.7	4	0.5	10	0.9	2	0.3
Inflammatory Arthropathies	33	1.0		0	0.0	8	1.8	8	0.9	13	1.2	4	0.6
Chronic kidney diseases	30	0.9		0	0.0	4	0.9	2	0.2	9	0.8	15	2.1
Bradycardias and conduction diseases	28	0.9		1	0.9	1	0.2	2	0.2	11	1.0	13	1.8
Cerebrovascular disease	27	0.8		0	0.0	2	0.5	8	0.9	11	1.0	6	0.8
Cardiac valve diseases	23	0.7		1	0.9	0	0.0	3	0.4	10	0.9	9	1.2
Parkinson and parkinsonism	18	0.6		0	0.0	0	0.0	3	0.4	10	0.9	5	0.7
Dyslipidemia	15	0.5		0	0.0	4	0.9	8	0.9	2	0.2	1	0.1
Peripheral neuropathy	15	0.5		0	0.0	4	0.9	5	0.6	3	0.3	3	0.4
Hermatological neoplasms	15	0.5		0	0.0	1	0.2	1	0.1	8	0.7	5	0.7
Other neurological diseases	13	0.4		1	0.9	3	0.7	2	0.2	6	0.6	1	0.1
Autoimmune diseases	13	0.4		0	0.0	3	0.7	4	0.5	3	0.3	3	0.4
Epilepsy	12	0.4		0	0.0	4	0.9	4	0.5	2	0.2	2	0.3
Cataract and other lens diseases	12	0.4		0	0.0	0	0.0	5	0.6	4	0.4	3	0.4
Other musculoskeletal and joint diseases	10	0.3		2	1.9	0	0.0	3	0.4	3	0.3	2	0.3
Glaucoma	9	0.3		0	0.0	0	0.0	3	0.4	3	0.3	3	0.4
Neurotic, stress-related and somatoform diseases	5	0.2		0	0.0	0	0.0	1	0.1	3	0.3	1	0.1
Thyroid diseases	5	0.2		0	0.0	0	0.0	2	0.2	2	0.2	1	0.1
Dementia	4	0.1		0	0.0	0	0.0	0	0.0	0	0.0	4	0.6
Chronic liver diseases	4	0.1		0	0.0	1	0.2	1	0.1	2	0.2	0	0.0
Osteoarthritis and other degenerative joint diseases	4	0.1		0	0.0	0	0.0	1	0.1	2	0.2	1	0.1
Deafness, hearing impairment	3	0.1		0	0.0	0	0.0	0	0.0	0	0.0	3	0.4
Inflammatory bowel diseases	3	0.1		0	0.0	0	0.0	3	0.4	0	0.0	0	0.0
Migraine and facial pain syndromes	2	0.1		0	0.0	0	0.0	2	0.2	0	0.0	0	0.0

Anemia	2	0.1		0	0.0	0	0.0	0	0.0	2	0.2	0	0.0
Solid neoplasms	2	0.1		0	0.0	0	0.0	0	0.0	1	0.1	1	0.1
Chronic pancreas, biliary tract and gallbladder diseases	1	0.0		0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Multiple sclerosis	1	0.0		0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Other genitourinary diseases	1	0.0		0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Schizophrenia and delusional diseases	1	0.0		0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Venous and lymphatic diseases	1	0.0		0	0.0	0	0.0	0	0.0	1	0.1	0	0.0
Blindness, visual impairment	0	0											
Chromosomal abnormalities	0	0											
Chronic ulcer of the skin	0	0											
Colitis and related diseases	0	0											
Other digestive diseases	0	0											
Other eye diseases	0	0											
Other skin diseases	0	0											
Prostate diseases	0	0											

[a] (COPD), emphysema, chronic bronchitis excludes J44 diagnosis

Modul 5

Pediatric solid organ injury - frequency of abdominal imaging is determined by the treating department

Zimmermann, P.; **Schmidt, T.**; Nelson, J.; Gosemann, J.-H.; Bassler, S.; Stahmeyer, J.; Hirsch, F.; Lacher, M.; Zeidler, J.

Medicine; 99:45
DOI: 10.1097/MD.0000000000023057

2020

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https://journals.lww.com/md-journal/fulltext/2020/11060/pediatric_solid_organ_injury___frequency_of.55.aspx

Modul 6

Determinants of colorectal cancer screening in Germany: a claims data analysis

Pardey, N.; Kreis, K.; **Schmidt, T.**; Stahmeyer, J.; Krauth, C.; Zeidler, J.

Zeitschrift für Gastroenterologie; 59(7):644-656
DOI: 10.1055/a-1480-8861

2021

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https://www.thieme-connect.com/products/ejournals/abstract/10.1055/a-1480-8861

Modul 7

Healthcare costs associated with breast cancer in Germany: a claims data analysis

Kreis, K.; Plöthner, M.; **Schmidt, T.**; Seufert, R.; Schreeb, K.; Jahndel, V.; Maas, S.; Kuhlmann, A.; Zeidler, J.; Schramm, A.

European Journal of Health Economics; 21:451-464
DOI: 10.1007/s10198-019-01148-w

2020

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ORIGINAL PAPER

Healthcare costs associated with breast cancer in Germany: a claims data analysis

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Abstract

Purpose This study estimates the healthcare costs associated with breast cancer (BC) for different treatment phases (initial, intermediate, terminal) in Germany from the payer's perspective.

Methods The analysis uses claims data from the AOK Bayern covering 2011–2014 for continuously insured BC patients identified through inpatient and outpatient diagnoses. We calculate the healthcare costs attributable to BC using a control group design comparing the target population to a 1:2 matched control group adjusted for age, gender, and comorbidities. For incident and prevalent BC cases, we calculate age-standardized phase-specific incremental costs stratified by cost domain.

Results The initial, intermediate, and terminal phases comprise 3841, 28,315, and 1767 BC cases, respectively. BC-related incremental costs follow a u-shaped curve, with costs highest near diagnosis and death, and lower in between. With average costs of €33,237 per incident and €28,211 per prevalent case in the remaining 11 months before death, the highest BC-related incremental healthcare costs can be found in the terminal phase. In the initial phase, there were mean incremental costs of €21,455 the first 11 months after diagnosis. In the intermediate phase, incremental costs totaled €2851 per incident and €2387 per prevalent case per year. Healthcare costs decreased with age in most phases. The cost drivers depend on the treatment phase, with cytostatic drugs and inpatient treatment showing the highest economic impact in most phases.

Conclusion The study concludes that BC care costs impose a relevant economic burden on statutory health insurance and vary substantially depending on the treatment phase.

Keywords Breast cancer · Disease cost · Claims data · Joinpoint · Germany

JEL Classification I10 · I13 · I14

Introduction

Breast cancer (BC) is the world's second most common type of cancer and the most frequent in women. It represents 12% of all new cancer cases and 25% of all cancers in women [1].

In 2014, the age-standardized rate of incidence for women was 114.6 per 100,000 people in Germany, representing 69,220 new BC cases. Between 1980 and 2004, the incidence rate increased by about 50% [2]. Moreover, 559,900 German women (10-year prevalence) were living with a BC diagnosis in 2014, and 17,670 of them died from the disease. However, the relative 5-year survival rate increased from 69% in 1980 to 81% in 2004 [3]. This improvement resulted from better treatment options (e.g., higher radiation doses [4]), new drug interventions [5], and earlier diagnoses (e.g., through mammography screening [6]).

The treatment and prognosis of BC are influenced by factors such as age, cancer stage, and tumor characteristics (status of estrogen receptor, progesterone receptor, human epidermal growth receptor 2, and the histologic grade) [7]. The disease stage (diseases stage 0–IV) influences

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disease-specific costs [8], which range from $60,637 (stage 0) to $134,682 (stage IV) per patient in the initial 12 months postdiagnosis. In the European Union, cancer incurred €126 billion of costs in 2009, €15 billion of which were attributable to BC. Accounting for 12% of total cancer costs, BC represents the second highest economic cancer burden [9]. Germany's costs of illness (COI) for BC were estimated at around 2169 million euros in 2015 [10]. Germany has Europe's highest BC healthcare costs per person [9].

Cost analyses are important for political decision making concerning prioritization and allocation [11]. Economic studies on BC cost patterns [12] include few analyses of BC-attributable health expenditures in Germany [13, 14]. Only two studies have reported the COI of BC using claims data from a statutory health insurance (SHI) in Germany [14, 15] of which one was only published as a poster abstract [15]. The second study is based on highly aggregated data sets referring to the year 1999 and covering inpatient spending, medication costs and sickness benefits, thus neglecting further cost domains (i.e., outpatient care, remedies/medical aids, rehabilitation). Moreover, stratification by cost category did not take place [14]. Claims data from SHIs are well suited for cost analyses, since they are routinely collected for billing and reimbursement. However, a detailed analysis of overall direct disease-related costs that identifies the cost-driving factors is required, because the extant studies differ substantially in their cost-calculation methods and cost domains considered.

Moreover, unlike US data [16], the German data have not been analyzed for cost patterns through a clinically meaningful phase-of-care approach in relation to diagnosis and death. The phases used by US studies are commonly divided into initial, intermediate and terminal care, and phase duration can be determined theoretically or empirically. This approach takes into account that costs may differ strongly across phases according to the need for treatment and healthcare costs are expected to be highest near diagnosis and death [16]. This is the first study that estimates the BC-attributable health expenditures in Germany according to empirically determined treatment phases.

Methods

Data source and study population

AOK Bayern provided data on all services reimbursed. Its sickness fund covered almost 4.3 million insured individuals in 2011 [17]. The analysis includes costs for inpatient and outpatient care, medication/cytostatic drugs, remedies and medical aids, rehabilitation, sick leave, and travel expenses. Patient identification was based on the ICD-10-GM system with ICD codes C50.0 to C50.9. Inclusion in the study population required documentation for at least one inpatient diagnosis or secured outpatient BC diagnosis in 2012. For exclusive identification by outpatient diagnosis, a second secured outpatient diagnosis was required within the following three quarters (i.e., occurring in 2013). We used 2011 to differentiate between incident and prevalent cases. Patients were defined as "incident" if no C50 diagnosis (outpatient/inpatient) was documented in 2011. All sample patients had to be continuously insured from 2011 to 2014 or until death (whichever came first). Male patients and patients under 18 were excluded, as both groups require special treatment.

Study design

We calculated BC-attributable costs using a control group design with pairwise direct matching. We compared BC patients to a 1:2 matched control group adjusted for gender, age and comorbidities. Using the Elixhauser comorbidity score [18], we calculated comorbidities for both the intervention and control groups in 2011 on the basis of at least one inpatient/secured outpatient diagnosis. To avoid overadjustment, BC diagnosis was excluded in the count. For matching, we used the nearest neighbor approach, allowing for a caliper of 5 years/points. The control sample consisted of females continuously insured by AOK Bayern from 2011 to 2014 without a BC diagnosis. Replacement of control group members was only allowed once.

Follow-up started for BC cases identified by hospitalization from the beginning of the month of the inpatient diagnosis. In German claims data, outpatient diagnoses are reported on a quarterly basis. Thus, within the quarter of each BC diagnosis, we defined the beginning of the month in which the first service date (according to the Uniform Valuation Scheme [EBM]) was documented as the approximate date of the index event. Follow-up ended in the latest 2 years following the index event or in the month of death, whichever came first. We ensured that all BC cases classified as "non-deceased" had not died within 6 months following the end of the observation. For controls, we considered follow-up periods analogously to the BC cases.

Following US studies [16, 19–25], we divided the time after BC diagnosis into clinically relevant treatment phases: (1) initial phase, comprising the primary course of therapy (e.g., surgery, chemotherapy, radiation); (2) intermediate phase, including active surveillance and ongoing medication to prevent recurrence (e.g., hormone blockade) or treatment complications derived from the initial course of therapy; and (3) terminal phase, comprising (palliative) services provided in the last months before death. Lacking a scientific consensus on the duration of BC treatment phases, we first calculated the monthly BC-attributable costs and examined the average cost patterns from diagnosis to death. Using Trend Analysis Software from the National Cancer

Institute [26], we applied joinpoint regression [22, 27] to determine the length of the initial and terminal phase by assessing the points at which statistically significant changes occur in the cost slope. According to joinpoint regression analysis, there must be at least 12–16 data points (months) to receive two joinpoints. As the observation period's maximum was 24 months and BC cases showed different characteristics (e.g., incident vs. prevalent, alive vs. deceased), not all individuals underwent all phases of care. Therefore, to determine the length of the initial phase, we examined average cost patterns of newly diagnosed BC cases that were observable for 18–24 months. Similarly, definition of terminal phase length was based on prevalent BC cases that had died during the observation period and were observable for 18–24 months preceding death.

After determination of phase care length, individuals were assigned to phases of care. Following the literature [22, 24], the observation period for BC cases who died was first assigned to the terminal phase of care. Any remaining time under observation, and all follow-up time for BC survivors, was then transferred to the initial treatment phase, and the most recent was assigned to the intermediate phase. In the initial and terminal phases, patients were excluded if they were not observable for the period determined by the joinpoint regression analysis. To be included in the intermediate phase, BC cases had to be observable for at least 12 months (costs are on an annual basis).

Calculation and presentation of healthcare costs

Copayments and out-of-pocket payments were not considered because costs were analyzed from the SHI perspective. Healthcare costs in euro were extracted from the database for both BC cases and controls. For each inpatient/rehabilitation stay and sick leave period, costs were divided by the length of stay/duration and calculated according to the start and end of each phase. Unfortunately, only annual outpatient care costs were available. To obtain monthly values, outpatient care costs were divided by the months under observation. To provide a better overview, the costs of cytostatic drugs and any remaining medication are reported separately. These medication costs include only prescriptions for outpatient care. The costs of drugs administered during inpatient episodes are part of total inpatient costs.

By comparing the cost differences between BC cases and controls, we could calculate the BC-attributable costs differentiated according to care phase. To adjust for age differences between SHIs, we standardized costs according to the 5-year age structure of compulsory insured women in Germany for 2011 using data from the Federal Ministry of Health [17]. As the cases were few, we aggregated the costs of BC cases younger than 45 (initial and intermediate phase) and younger than 50 (terminal phase) before standardization.

Sensitivity analyses were also conducted, calculating standardized healthcare costs by treatment type for the initial and terminal phase of care. Patient allocation to treatment types was based on clinical knowledge defining codes for surgery, radiotherapy and chemotherapy (see Appendix 1). Inclusion required at least one healthcare service. Data management and statistical analyses were performed with SAS 9.4.

Results

Study population

The inclusion criteria produced 36,033 BC patients (see Fig. 1). Of these, 32,058 were matched to 64,116 controls (1:2) and followed for a maximum of 2 years. After the matching, no significant differences were observed between BC cases and the controls concerning gender, age, or comorbidity score (see Table 1). Overall, 13% of BC cases were identified as incident, and 6% died within the follow-up period.

Through the joinpoint regression analysis, the initial treatment phase was defined as the month of diagnosis and the following 10 months. The terminal phase comprised the last 11 months of life, and the intermediate phase comprised all months between the initial and terminal phases. In the initial and terminal phase, the joinpoint regression analysis identified the points at which BC-related costs decreased

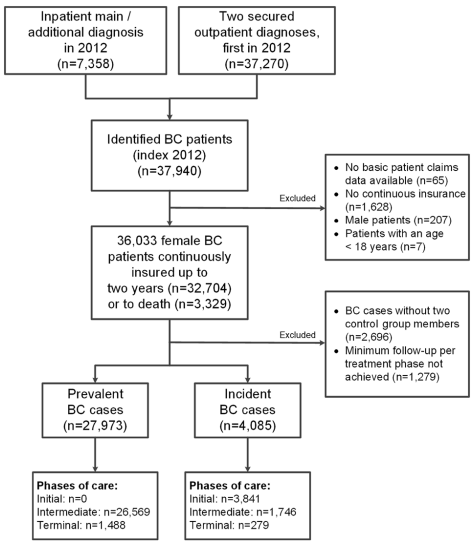

Fig. 1 Cohort selection

Table 1 Demographic characteristics after matching

Group	Gender: female		Age		Elixhauser comorbidity score		*n*
	%	p^a	Mean [SD]	p^b	Mean [SD]	p^b	
BC cases	100	1	67.12 [12.17]	0.99	5.93 [8.67]	0.99	32058
Controls	100		67.13 [12.16]		5.93 [8.67]		64116

SD standard deviation

[a]Chi-square test

[b]U test following Mann and Whitney

significantly. BC cases were included in one (94%) or two (6%) phases of care. Survivors were followed for 23 months on average (SD = 1) and deceased individuals 17 months (SD = 4) on average.

Concerning demographic characteristics, Table 2 shows that age at phase onset averaged around 67 in the initial phase, 67 (incident cases) versus 68 years (prevalent cases) in the intermediate phase, and 77 (incident cases) versus 76 years (prevalent cases) in the terminal phase. The mean Elixhauser score was 4 points for BC cases in the initial phase, 4 (incident cases) versus 6 (prevalent cases) points in the intermediate phase and was highest for individuals assigned to the terminal phase (7 versus 13 points). Within each phase, prevalent cases had a significantly higher comorbidity score than incident individuals ($p < 0.001$; Mann–Whitney *U* test).

Healthcare costs

The highest incremental BC costs are in the terminal phase, followed by the initial and intermediate phases. Tables 3 and 4 show the age-standardized healthcare costs in euro per cost component within each treatment phase for incident and prevalent patients.

As Table 3 shows, in the first 11 months following diagnosis, the average BC-related incremental costs totaled €21,455 per patient. At €11,220 per patient, cytostatic drugs represent more than half (52%) of initial phase costs, followed by inpatient care (23%), outpatient care (11%), and sick leave payments (8%). All remaining cost compounds are of minor importance. Subgroup analyses revealed that total initial phase costs varied substantially by treatment type (see appendix 2). Incremental costs totaled €60,000 in patients treated with surgery, radiotherapy and chemotherapy, whereas incremental costs of those treated with surgery alone (€7874) or surgery and radiotherapy (€11,210) were much lower.

In the intermediate phase, there were €2851 mean BC-related incremental costs for incident and €2387 for prevalent patients per year. For incident BC cases, almost a third of the costs is attributable to outpatient care. Cytostatic drugs, inpatient care, and sick leave payments each accounted for 15–20% of incremental BC-related costs. In contrast, accounting for over half of incremental costs in prevalent cases, the highest cost drivers are cytostatic drugs, followed by outpatient care (18%), inpatient care (14%), and remedies/medical aids (9%). In both incident and prevalent cases, all remaining medication, rehabilitation, and travel expenses have limited effects on incremental costs.

In the terminal phase (11 months before death), mean BC-related incremental costs totaled €33,237 in incident and €28,211 in prevalent cases. In both incident and prevalent cases, nearly half of the costs were attributable to inpatient care, followed by cytostatic drug treatment (accounting for 29–34%). Differentiating phase costs by treatment type, subgroup analyses showed that total terminal care costs ranged between €11,608 in patients without active therapy (no claim for surgery, radiotherapy and chemotherapy) and €52,651 in those treated with radiotherapy and chemotherapy (see Appendix 3).

Several studies suggest that BC costs differ substantially by age [13, 14]. Given the unstandardized costs stratified by 5-year age groups (see Appendices 4 and 5), incremental BC-related costs in the initial phase decreased substantially by age, with €56,169 in patients aged 30–34 compared to €4530 in patients aged 85 or older. Though not apparent in all 5-year age groups, this general trend is also evident in the intermediate and terminal phases.

Discussion

Cancer costs are typically first reported at the initial diagnosis, for a specific event like recurrence, or generally (for cancer survivors) in a specific year. However, costs may change over time when measured longitudinally starting from initial cancer diagnosis to long-term survival or death. In the US, phase-specific approaches are often used to analyze cancer cost patterns [16, 25]. This study used claims data on real-life treatment to estimate the costs of BC care for Germany according to clinically relevant treatment phases. Using definitions of treatment phases according to joinpoint regression analysis, our study suggests that incremental BC-related costs differ substantially by care phase. Standardized

Table 2 Baseline characteristics of BC cases

Phase	Age (at phase onset)					Elixhauser comorbidity score					
	Mean	[SD]	Median	Min	Max	Mean	[SD]	Median	Min	Max	*n*
Initial											
Incident	66.78	[13.15]	68	21	101	3.99	[7.31]	1	− 11	49	3841
Intermediate											
Incident	67.03	[13.12]	69	21	102	3.84	[7.29]	0	− 10	49	1746
Prevalent	67.81	[11.83]	69	19	107	5.81	[8.57]	3	− 14	58	26569
Terminal											
Incident	76.97	[13.35]	80	23	100	7.15	[8.42]	6	− 7	39	279
Prevalent	76.49	[11.75]	78	37	100	13.35	[10.16]	12	− 7	49	1488

SD standard deviation

Table 3 Age-standardized healthcare costs of incident BC cases in Germany (in €, mean [standard deviation])

Cost sector	Initial phase (11 months)						Intermediate phase (12 months)						Terminal phase (11 months)					
	BC cases		Controls		Increment		BC cases		Controls		Increment		BC cases		Controls		Increment	
Medication (sum)	12043	[24100]	495	[1723]	11548	[24227]	1186	[7070]	491	[1516]	695	[7237]	11971	[22320]	690	[3915]	11281	[22696]
Cytostatic drugs	11224	[23676]	4	[165]	11220	[23679]	577	[6769]	0		577	[6769]	9805	[21863]	0		9805	[21863]
Other medication	819	[2021]	491	[1702]	328	[2637]	609	[1848]	491	[1516]	118	[2383]	2166	[3529]	690	[3915]	1476	[5389]
Remedies/medical aids	525	[1090]	231	[578]	295	[1220]	573	[1144]	289	[767]	283	[1368]	1247	[1685]	279	[837]	969	[1817]
Outpatient care	3119	[2541]	765	[615]	2353	[2626]	1736	[1620]	850	[642]	886	[1761]	3528	[3065]	853	[751]	2675	[3186]
Inpatient care	6141	[7111]	1160	[4254]	4982	[8303]	1864	[4515]	1383	[4493]	482	[6376]	16513	[14745]	1024	[2810]	15488	[15125]
Rehabilitation	178	[734]	81	[513]	97	[882]	118	[627]	94	[578]	24	[850]	357	[1355]	91	[497]	266	[1448]
Sick leave payments[a]	1862	[4421]	126	[1051]	1736	[4483]	560	[2094]	111	[885]	448	[2224]	1643	[4033]	61	[525]	1581	[3909]
Travel expenses	508	[860]	64	[332]	444	[923]	112	[392]	80	[398]	32	[555]	1031	[1241]	55	[205]	976	[1266]
Sum	24377	[29560]	2922	[5686]	21455	[30297]	6149	[10186]	3298	[5889]	2851	[11823]	36289	[30060]	3052	[6372]	33237	[31236]

[a]If an illness lasts longer than 6 weeks, the employee will receive sick leave payments from the health insurance covering 70% of the gross salary for up to 78 weeks

Table 4 Age-standardized healthcare costs of prevalent BC cases in Germany (in €, mean [standard deviation])

Cost sector	Intermediate phase (12 months)						Terminal phase (11 months)					
	BC cases		Controls		Increment		BC cases		Controls		Increment	
Medication (sum)	1890	[10128]	568	[1642]	1322	[10229]	12,003	[23427]	643	[1982]	11360	[23427]
Cytostatic drugs	1220	[9654]	7	[284]	1213	[9657]	9698	[22836]	6	[359]	9692	[22840]
Other medication	670	[1857]	561	[1610]	109	[2427]	2306	[3460]	638	[1943]	1668	[3959]
Remedies/medical aids	511	[890]	305	[856]	206	[1208]	1238	[1542]	416	[1187]	822	[1931]
Outpatient care	1295	[1191]	871	[716]	424	[1376]	2876	[2557]	872	[710]	2005	[2683]
Inpatient care	1684	[4539]	1353	[3556]	330	[5711]	14,914	[15460]	1885	[5466]	13029	[16567]
Rehabilitation	95	[469]	92	[449]	3	[638]	202	[906]	98	[547]	103	[1056]
Sick leave payments[a]	214	[1166]	141	[936]	73	[1479]	298	[1532]	139	[1339]	158	[1978]
Travel expenses	105	[368]	77	[324]	27	[481]	834	[1078]	99	[435]	735	[1151]
Sum	5794	[12561]	3407	[5201]	2387	[13443]	32,365	[30141]	4153	[7752]	28211	[30612]

[a]If an illness lasts longer than 6 weeks, the employee will receive sick leave payments from the health insurance covering 70% of the gross salary for up to 78 weeks

BC-attributable costs were highest in the terminal phase (11 remaining months before death), averaging around €33,237 in incident cases and €28,211 in prevalent case. Initial care costs in the 11 months after diagnosis totaled €21,455. Costs of €2,851 for incident and €2,387 for prevalent cases were incurred each year in the intermediate phase. Average costs in the intermediate phase are significantly lower ($p < 0.001$; Wilcoxon rank sum test) than for the initial and terminal phase. Consistent with US BC studies, the costs follow a u-shaped curve, with costs highest near diagnosis and death, and lower in between. Comparing absolute costs with US data would be challenging due to differences in treatment structures and reimbursement schemes as well as methodological inconsistencies (e.g., in data sources, study populations, matching criteria, and phase selection methods).

European studies that have not applied a data-driven phase-of-care approach have also found that the economic burden of BC is highest in the periods following diagnosis and near death [13]. With standardized costs of €21,455 per person for the first 11 months after diagnosis, initial care costs in our study are much higher than are those in other studies. Based on German claims data, Damm et al. [15] reported that BC-attributable costs averaged around €4,300 per person in the 1st year after diagnosis. The 12-month costs of initial care have been reported to total around €8553 for Sweden (converted from SEK to € with an average 2005 exchange rate of 9.2822 SEK/€) [28]) and €7982 for Belgium [29]. However, studies differ in their data sources and cost-calculation methods, as well as in the cost domains examined, leading to an underestimation of costs. Moreover, BC healthcare costs per case [30]/per person in the EU [9] are generally found to be more than two to three times higher in Germany than in Belgium or Sweden.

For the intermediate phase, annual direct BC-related healthcare costs were estimated at €2851 for incident and €2387 for prevalent cases. While Broekx et al. [29] reported much lower costs for the 2nd year following diagnosis (€1317 per patient for Belgium), our results are in line with Lidgren et al.'s [28] finding that annual direct costs for the 2nd and following years after initial BC diagnosis /recurrence totaled €2359 (converted from SEK to € with an average 2005 exchange rate of 9.2822 SEK/€). Moreover, our results indicate that incident cases result in a significant ($p < 0.001$; Mann–Whitney U test) average cost impact of about €460 per year compared to prevalent cases. Given the proximity in time to the primary diagnosis, active surveillance and therapy for complications resulting from the initial course of therapy might be paramount. In prevalent cases, more than half of the costs are attributable to cytostatic drugs, indicating that our sample might include BC cases experiencing recurrent events. Although BC costs are generally higher near diagnosis and death, intermediate phase costs will become increasingly economically important, even if patients remain recurrence-free, as BC is showing increasing survival rates. Further examination of whether intermediate care costs will decline after initial diagnosis, as reported by Broekx et al. [29], is required.

Few studies have examined mortality costs. In the 11-month terminal phase of care, direct BC-related healthcare costs averaged €33,237 in incident cases and €28,211 in prevalent cases. The only German study that calculated BC costs in the terminal phase found, by applying the propensity score method and adjusting for age and comorbidities, incremental direct healthcare costs of €10,950 in the last year before death [15]. However, unlike our analysis, this study did not include all cost domains from the perspective of the SHI and performed one-to-one matching to balance patient characteristics between cases and controls. The choice of comparison cohort can strongly impact the net costs of cancer [31], but the scientific literature displays

no broad consensus on the choice of comparison group in cancer cost estimation. As healthcare costs vary strongly, depending on comorbidities and resource consumption, one-to-two matching may lead to more robustness in estimation.

Concerning direct costs, most studies report inpatient care [13, 15, 32] or both inpatient care and drugs [9] as the greatest cost drivers in BC. Our results suggest that the cost-driving factors depend on the care phase. In the initial phase, cytostatic drug costs were the main driver, whereas in the terminal phase inpatient treatment was paramount. The impact of cytostatic drugs in the intermediate phase was greater for prevalent (51%) than for incident (20%) patients. Inpatient care costs contributed to 23% of costs in the initial phase and 14–17% in the intermediate phase. The differences in the economic relevance of inpatient care and medication might reflect the fact that cytostatic drug costs represent only outpatient prescriptions and that chemotherapy might also be administered during an inpatient episode and thus be included in inpatient costs.

Consistent with previous German studies [13, 14], we found that direct BC-attributable costs decreased with age, particularly in the initial treatment phase (see Appendix 4 and 5). Older women might have a lower chance of receiving aggressive treatment due to comorbidities or lower expected long-term benefits, or because they reject chemotherapy. Similar to Gruber et al. [14], we found that, while 97% of healthcare costs were BC-attributable in 25–29-year-old women, the share decreased to 56% in women over 85. In the intermediate phase, the share decreased from 77 to 23% in incident and from 71 to 15% in prevalent cases. Younger women might be more likely to take time off from work after diagnosis and, as they receive more aggressive treatment, may also experience more lasting effects from the initial therapy. Hence, if BC could be detected earlier or even prevented, especially among young women, the overall cost burden could be reduced.

This study is limited by the nature of its data source. First, as claims data are routinely collected for billing and reimbursement, they do not include information on clinical parameters, thus preventing cost stratification by cancer stage or tumor type. However, we differentiated between incident and prevalent patients as well as different treatment types. As patient allocation to treatment cohorts (subgroup analyses) was based exclusively on services reimbursed by SHI and some services/drugs are not indication-specific (e.g., methotrexate), some patients might not have been (adequately) captured. However, consulting a clinical expert, we developed an algorithm using a wide range of different classification systems. Moreover, with regard to the differentiation of incident and prevalent cases, using a lookback period of 1 year might overestimate incident BC cases. Nevertheless, when performing sensitivity analyses identifying BC cases in 2013 ($n = 37{,}824$) and extending the lookback period from 1 to 2 years, we found a small decrease in the percentage of incident patients from 13.5% (1 year) to 12.0% (2 years).

Second, claims data lack information on cause of death. Hence, BC cases assigned to the terminal phase might have died from causes other than BC. Third, as only annual (calendar year) outpatient care cost data were available, monthly costs might not have been assigned adequately to the care phases. However, in the 12-month intermediate phase, more than 80% of the individuals started their phase in the first quarter of 2012, covering almost the full calendar year. Fourth, sick leave payments include exclusively SHI costs. German law requires that an employee will only receive sick leave payments from the health insurance (covering 70% of the gross salary for up to 78 weeks) if an illness lasts longer than 6 weeks. During the first 6 weeks of sickness, the employer has to pay 100% of the salary. Fifth, we used data from one regional sickness fund. As the composition of health insurances differs (e.g., in terms of age, gender and social status [33, 34]) our results' generalizability might be limited. The median age at diagnosis and death was about 3 and 5 years, respectively, above the median age reported in registry data [3], because the AOK Bayern included a higher proportion of insured women 70 or older and a lower proportion of insured women 30–70 relative to all statutory insured women in Germany in 2011 [17]. To address this issue and generalize costs, we standardized them according to gender and the 5-year age structure of the German health insurance population. We thus calculated BC-related incremental costs under real-life conditions, including all cost domains that might be relevant from the SHI perspective. Ours is the first study to calculate direct BC costs for Germany using an incidence-based phase-of-care approach.

Conclusion

The economic burden of BC represents a major challenge for the SHI. This study indicates that BC healthcare costs depend on treatment phase, with higher costs near diagnosis and death and lower costs in between. The greatest economic burden occurs in the first 11 months following diagnosis and the last 11 months before death, depends heavily on patient age, with cytostatic drugs and inpatient care accounting for three quarters of total costs. Although intermediate phase costs are lower than those in phases near diagnosis and death, they remain substantial. Future studies should stratify German BC care costs according to cancer stage and tumor characteristic by linking claims data with clinical information.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Appendix 1

See Table5

Table 5 Claims defining treatment typesin BC patients

Code	System	Name/description
Chemotherapy[a]		
9999092	PZN	Cytostatic drugs (parental preparations)
L01XA01	ATC	Cisplatin
L01DB01	ATC	Doxorubicin
L01DB03	ATC	Epirubicin
L01DB07	ATC	Mitoxantrone
L01AA09	ATC	Bendamustine
L01XC07	ATC	Bevacizumab
L01BC06	ATC	Capecitabine
L01AA01	ATC	Cyclophosphamide
L01XX41	ATC	Eribulin
L01BC02	ATC	Fluorouracil
L01BC52	ATC	Fluorouracil, combinations
L01BC05	ATC	Gemcitabine
L01XA02	ATC	Carboplatin
L01CD01	ATC	Paclitaxel
L01CD03	ATC	Paclitaxel poliglumex
L01CD02	ATC	Docetaxel
L01CA04	ATC	Vinorelbine
L01AA06	ATC	Ifosfamide
L01BA01	ATC	Methotrexate
L01DC03	ATC	Mitomycin
L01XX17	ATC	Topotecan
L01DC04	ATC	Ixabepilone
L01CA03	ATC	Vindesine
8–54	OPS	Cytostatic chemotherapy, immunotherapy and antiretroviral therapy
Surgery[a]		
5–87	OPS	Excision and resection of breast
5–88	OPS	Other mammary operations
5–40	OPS	Lymphatic tissue operation
J01Z	DRG	Tissue transplantation with microvascular anastomisation in case of malignant neoplasms of skin, subcutis and breast
J06Z	DRG	Mastectomy with prosthesis implantation and plastic surgery in case of malignant neoplasms
J07A	DRG	Minor interventions of the breast with axillary excision of lymphatic nodes or extremely severe or severe complication or comorbidity in case of malignant neoplasms, with intervention on both sides
J07B	DRG	Minor interventions of the breast with axillary excision of lymphatic nodes or extremely severe or severe complication or comorbidity in case of malignant neoplasms, without intervention on both sides
J08C	DRG	Skin graft or debridement without complex procedure, with specific intervention on the skin, subcutis and breast, with extremely severe complication or comorbidity
J10A	DRG	Plastic surgery of skin, subcutis and breast in case of malignant neoplasms
J14A	DRG	Plastic reconstruction of the breast in case of BNB with complex reconstruction or mastectomy on both sides in case of BNB or radiotherapy with oper. proc. in case of diseases and disorders of the skin, subcutis and breast, with prosthesis implantation on both sides or skin expander implantation
J14B	DRG	Plastic reconstruction of the breast in case of malignant neoplasms without complex reconstruction

Table 5 (continued)

Code	System	Name/description
J16A	DRG	Mastectomy on both sides in case of malignant neoplasms
J23Z	DRG	Major interventions on the breast in case of malignant neoplasms without complex intervention, without specific intervention on female reproductive organs in case of malignant neoplasms
J25Z	DRG	Minor interventions on the breast in case of malignant neoplasms without or extremely severe or severe complication or comorbidity
J26Z	DRG	Plastic reconstruction of the breast with complex skin graft or major intervention on the breast in case of malignant neoplasms with complex intervention or specific intervention on female reproductive organs in case of malignant neoplasms
J62A	DRG	Malignant neoplasms of the breast, more than 1 day of hospitalization, with extremely severe complication or comorbidity
J62B	DRG	Malignant neoplasms of the breast, 1 day of hospitalization or extremely severe complication or comorbidity
Radiotherapy[a]		
8–52	OPS	Radiotherapy
8–530	OPS	Therapy with open radionuclides
25211	EBM	Radiotherapy: flat fee in case of malignant neoplasms
25310	EBM	Soft X-ray or orthovoltage therapy
25320, 25321, 25322, 25323	EBM	High-voltage therapy
25330, 25331, 25333	EBM	Bracytherapy
40840, 40841	EBM	Lump sum for individual adjustments in case of radiotherapy (e.g. positioning aids)

PZN pharmaceutical registration number, *ATC* anatomical therapeutic chemical classification, *OPS* classification for the encoding of operations, procedures and general medical measures, *DRG* diagnosis-related groups, *EBM* catalogue of the Uniform Value Scale

[a]Inclusion required at least one healthcare service

Appendix 2

See Fig. 2

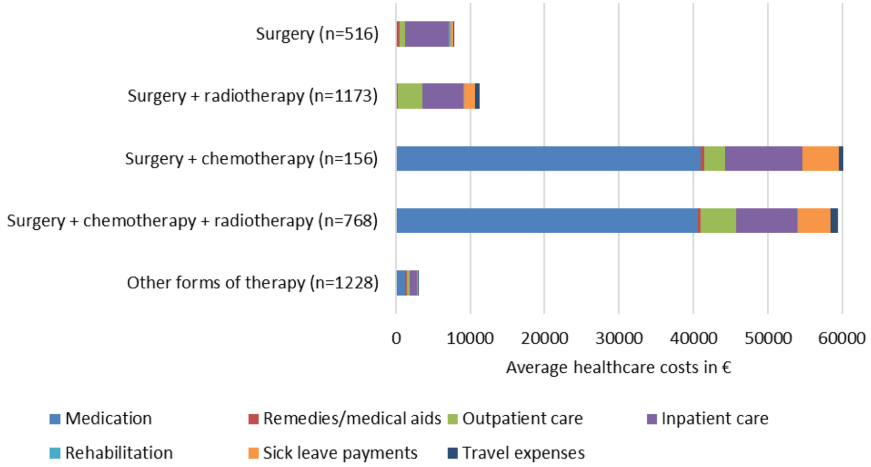

Fig. 2 Age-standardized incremental healthcare costs of BC cases in the initial phase by treatment type (in €, mean). As cases were few we aggregated BC cases with radiotherapy ($n=68$) or chemotherapy ($n=33$) or radiotherapy + chemotherapy ($n=17$) or no active therapy ($n=1110$) to "other forms of therapy". The group "no active therapy" includes all BC cases without any claim for surgery, radiotherapy and chemotherapy

Appendix 3

See Fig. 3

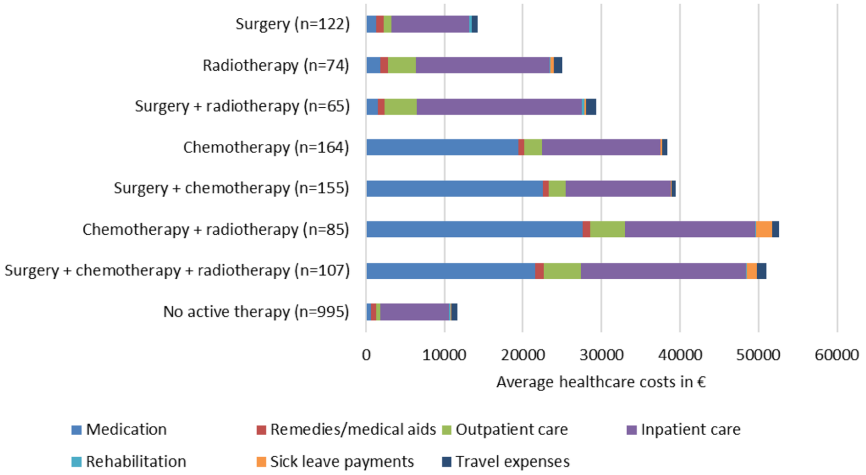

Fig. 3 Age-standardized incremental healthcare costs of BC cases in the terminal phase by treatment type (in €, mean). The group "no active therapy" includes all BC cases without any claim for surgery, radiotherapy and chemotherapy

Appendix 4

See Table 6

Table 6 Unstandardized healthcare costs of incident BC cases (*n*) in Germany by age group (in €, mean [standard deviation])

Age	Initial phase (11 months)							Intermediate phase (12 months)							Terminal phase (11 months)						
	n[a]	BC cases		controls		Increment		n[a]	BC cases		controls		Increment		n[a]	BC cases		controls		Increment	
< 20																					
20–24	6	12380	[27084]	2275	[4778]	10106	[22876]	2	1645	[1930]	687	[454]	959	[1247]	1	14315		362	[256]	13954	[256]
25–29	13	55784	[48537]	1512	[2256]	54273	[46892]	8	8765	[8657]	1995	[2234]	6769	[9236]							
30–34	26	58166	[55411]	1997	[4147]	56169	[54360]	15	6201	[5657]	1245	[1308]	4956	[5974]	3	39466	[16105]	4482	[6279]	34984	[17635]
35–39	58	47073	[34753]	1554	[1723]	45520	[34727]	24	8030	[6232]	2209	[3773]	5821	[7011]	1	46219		6244	[7550]	39975	[7550]
40–44	125	42923	[39533]	2373	[4518]	40550	[39680]	61	6316	[10138]	2645	[4715]	3671	[11048]	4	70818	[9948]	1864	[1632]	68954	[9184]
45–49	262	37070	[34548]	2258	[4319]	34812	[34483]	127	6641	[7734]	2489	[5257]	4152	[9183]	6	73724	[35729]	1744	[1965]	71980	[34894]
50–54	350	32299	[32725]	2587	[5766]	29711	[33316]	162	7381	[14994]	2607	[4789]	4774	[15765]	11	39262	[19836]	1818	[2368]	37444	[19665]
55–59	364	29207	[33346]	2988	[5562]	26218	[34108]	168	5262	[7208]	2523	[3930]	2739	[8250]	13	53116	[36986]	3115	[5605]	50000	[37103]
60–64	485	23409	[28398]	2599	[4218]	20810	[28804]	231	6592	[16187]	3012	[5452]	3580	[17148]	15	48134	[42877]	4425	[14797]	43709	[45887]
65–69	446	18389	[21133]	3288	[9093]	15101	[23064]	209	4976	[8811]	3706	[6976]	1270	[11346]	18	32434	[21911]	2406	[3084]	30028	[22561]
70–74	604	17213	[18705]	2873	[5520]	14340	[19341]	266	5990	[9313]	3542	[5937]	2448	[11065]	31	29079	[17431]	3769	[4485]	25310	[17602]
75–79	524	13049	[12921]	3856	[5854]	9193	[14387]	233	5494	[7853]	3824	[5837]	1669	[9766]	40	25067	[23894]	2938	[5432]	22129	[24596]
80–84	333	10551	[9669]	3624	[5908]	6927	[11083]	150	6686	[9263]	5464	[9768]	1222	[13818]	55	17776	[16291]	3335	[4398]	14442	[17385]
> 84	245	8020	[9320]	3490	[4581]	4530	[10518]	90	5590	[5758]	4315	[5035]	1275	[7410]	81	10214	[6666]	3355	[4256]	6860	[7712]

[a]number of BC cases

Appendix 5

See Table 7

Table 7 Unstandardized healthcare costs of prevalent BC cases (*n*) in Germany by age group (in €, mean [standard deviation])

Age	Intermediate phase (12 months)							Terminal phase (11 months)						
	n[a]	BC cases		controls		Increment		n[a]	BC cases		controls		Increment	
< 20	1	2815		2093	[1592]	722	[1592]							
20–24	7	9269	[15984]	1592	[1311]	7677	[14712]							
25–29	28	6941	[13800]	2040	[3346]	4901	[14559]							
30–34	90	12790	[24404]	2489	[3457]	10301	[24508]							
35–39	199	9607	[22449]	2730	[5458]	6877	[23196]	7	84436	[39194]	4111	[6556]	80324	[39268]
40–44	663	7825	[20122]	2861	[5240]	4965	[20461]	10	37061	[17529]	3586	[5505]	33475	[17772]
45–49	1295	6738	[19038]	2708	[4935]	4030	[19654]	33	37403	[23323]	5678	[13748]	31725	[26243]
50–54	2248	5472	[10925]	3131	[5922]	2341	[12145]	46	57206	[42144]	4070	[8522]	53135	[39679]
55–59	2686	5178	[11441]	3320	[5319]	1858	[12304]	74	42479	[36820]	4457	[7580]	38022	[37378]
60–64	3304	5094	[10517]	3045	[4815]	2049	[11482]	101	30722	[18845]	3470	[8066]	27253	[21178]
65–69	3609	5416	[11111]	3383	[5403]	2033	[11937]	120	32262	[27941]	4289	[8731]	27974	[29468]
70–74	5202	5296	[8752]	3634	[4891]	1662	[9836]	219	25412	[19748]	3608	[4901]	21804	[20670]
75–79	3636	5571	[8364]	4116	[5607]	1455	[9886]	250	21973	[20860]	4417	[5872]	17556	[21411]
80–84	2191	5330	[6456]	4265	[4900]	1065	[7977]	273	15843	[12530]	4183	[5494]	11661	[13530]
> 84	1410	4928	[5123]	4166	[4600]	763	[6722]	355	10745	[9087]	3714	[4781]	7031	[10069]

[a] number of BC cases

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Modul 8

Portfolio structure of the German households and the role of insurance and pension entitlements

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ABHANDLUNG

Portfolio structure of the German households and the role of insurance and pension entitlements

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Abstract This paper examines the wealth structure of German households from 1975 to 2014 with special reference to the asset class insurance and pension entitlements. Therefore we use a unique dataset of Deutsche Bundesbank and apply a Financial Almost Ideal Demand System (FAIDS). We find a nearly proportional reaction of the insurance share to changes in the total wealth level, but no significant impact of the insurance return to the asset class. Therefore we conclude that security and not return optimization is the main demand motive for the asset class insurance and pension entitlements. Finally, we find a positive relation between the share of the elderly in Germany and the insurance share in the portfolio.

Die Rolle der Assetklasse „Lebensversicherung“ in der Portfoliostruktur privater Haushalte in Deutschland

Zusammenfassung In unserem Beitrag untersuchen wir die Frage, welche Determinanten langfristig die Struktur der Portfolios privater Haushalte in Deutschland beeinflussen, wobei die Analysen mit dem Fokus auf den Bereich Versicherungen durchgeführt werden. Grundlage hierfür ist ein Datensatz, welcher es erlaubt das System über den Zeitraum von 1975 bis Anfang 2014 auf Quartalsbasis zu betrachten. Hierzu wird ein Financial Almost Ideal Demand System (FAIDS) unter Berücksichtigung von externen makroökonomischen Einflüssen geschätzt. Aufgrund der Charakteristika von Lebensversicherungsprodukten erwarten wir, dass die Elastizitäten bzgl. der Versicherungsansprüche weniger elastisch sind als die der

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übrigen Anlageklassen. Die Ergebnisse stützen unsere Hypothese, da sie zwar eine annähernde Proportionalität zwischen dem Versicherungsanteil und dem Gesamtvermögen zeigen, jedoch keinen signifikanten Zusammenhang bezüglich des Einflusses des Versicherungszinses.

1 Introduction

In this paper we aim to answer the question which factors determine the structure of the German household portfolios in the long run. We especially focus on insurance and pension entitlements in this context. In the last forty years the capital allocation framework for private households in Germany has changed radically. Legislative changes for several asset classes and different economic cycles affect the capital allocation of private households. Especially the phase of low interest rates since the recent financial crisis should lead to an adjustment of private households' portfolio. Moreover the German reunification leads to a different macroeconomic framework and influences the portfolios of German private households in general.

In 2014, the overall wealth level of German private households was about EUR 5206.7 bn, whereas the share of insurance claims is about 38% and therefore the most important asset class. Nevertheless there is a poor understanding of the factors, which drive the investment decisions in insurances. In other words this paper will examine what the unique characteristics of insurance products compared with other asset classes are. We apply a Financial Almost Ideal Demand System (FAIDS) to identify the long run wealth elasticity and the elasticity between insurance entitlements and other asset classes.

The paper is organized as the following: Sect. 2 provides the theoretical background of the portfolio decisions of private households and shows the empirical evidence of FAIDS. Sect. 3 presents the data and methods used. Sect. 4 shows the results, which are discussed in Sect. 5. Sect. 6 concludes the paper.

2 Theoretical background of households portfolio structure and empirical evidence of the FAIDS

Brainard and Tobin (1968) built one of the first econometric models to explain the portfolio decision of the private households. Starting from an optimal risk and return portfolio, whereby every asset class is characterized by a specific risk-return profile. Any changes of return or risk exposure of a single asset, e. g. because of monetary policies, lead to the reconstruction of the portfolio. In his popular article "A General Equilibrium Approach To Monetary Theory" Tobin (1969) presents the framework of this type of econometric models for capital allocation. Tobin applies an equilibrium approach[1] and discusses the implications, e. g. the interdependence between the "financial" as well as the "real" side of an economy.

[1] In the sense of Walras law.

The development of the Almost Ideal Demand System (AIDS) by Deaton and Muellbauer (1980) gives a new drive into modeling the financial asset demand of private households. AIDS consists of demand equations for each asset class and is estimated simultaneously, including potential substitutions. Originally, AIDS was developed for modeling the demand of material goods, but the usage of the AIDS was soon extended to financial goods, for example by Weichert and Zietz (1986). They investigated empirically the financial investment of the private households in Germany from 1972 to 1984. Weichert/Zietz constructed five asset classes: Saving deposits by banks, time deposits, bonds, stocks and insurance entitlements. They found out that the share of insurance entitlements is only sensitive to the changes of wealth and does not react to interest rate changes of the other assets.[2] Weichert/Zietz concluded that insurance entitlements are long-term investments with relatively high cancellation costs.

Barr and Cuthberston (1991) used AIDS to examine the demand of liquid assets for the personal sector in the UK and extended the AIDS approach de facto to the Financial Almost Ideal Demand System handling financial goods. They present basic considerations for the use of AIDS for financial assets, e. g. the features of financial asset demand, like the aspect of liquidity; the question of maximizing the utility or minimizing the costs to achieve a given level of utility (duality approach)[3]. Moreover, Barr/Cuthberston discussed the inclusion of the total wealth level, the limitation of all neoclassical models e. g. the neglect of uncertainty, the requirement of separation between liquid assets and the role of inflation. Finally they estimated AIDS with five asset classes: Notes and coins, Sight deposits, Time deposits, Building society deposits and National savings investment account. They found that the effect of inflation for notes and coins and sight deposits is negative in the long run and causes a switch in the time deposits and building society deposits.

Blake (2004) presented the theoretical framework to extend the AIDS idea to financial goods. He estimated a real Financial Almost Ideal Demand System (FAIDS) to investigate the allocation of wealth in the personal sector in the UK. He covers the period of 1948 to 1994 and he distinguishes these five asset classes: net financial wealth, housing wealth, state pension wealth, private pension wealth and human capital, whereby the asset class human capital is modeled as the present value of the expected career earnings of the whole adult population. Blake finds that wealth effects are more important than relative returns. Moreover, he concludes that the net financial wealth, housing wealth and private pension wealth are complementary, while the state pension wealth is a substitute for all three of the mentioned asset classes.

Avouyi-Dovi et al. (2011) provided an analysis of the French household's financial portfolio structure with FAIDS. Beside the univariate approach in the form of an error correction model, their multivariate FAIDS approach covers six asset classes. Life insurance contracts are summarized in the category of "Insurance-debt securities" in addition to debt securities and so called D'épargne Populaire banking plans.

[2] Weichert and Zeitz (1986, p. 12).

[3] For this duality approach, see Conrad (1980). He applies the duality approach to answer a similar question, namely the allocation of assets and liabilities of the West-German Private Non-Bank Sector.

Avouyi-Dovi et al. estimated an unconstraint (without the symmetry and homogeneity restriction) and a constraint version of their FAIDS. Moreover, they included exogenous variables e. g. the dependency ratio defined as the number of people of ages 65 or older divided by the whole population. They found positive long-run elasticities for the dependency ratio on the asset class "Insurance-debt securities" as well as positive long-run elasticities for the insurance asset class for the constraint and the unconstraint FAIDS models.

Ramb and Scharnagl (2011) used a new data set from the Deutsche Bundesbank, which covers the wealth structure of the German households for the time period of 1959 to 2009 respectively in the West of Germany and as of 1991 Germany as a whole. They constructed eight asset classes: currency and transferable deposits, deposits with building and loan associations, debt securities, mutual funds shares, time deposits, saving deposits, shares and insurance and pension entitlements. Ramb/Scharnagl found that, in contrast to Linderkamp (2015), the sensitive reactions of private households' changes in the interest rate level. Overall, they showed positive own-rate elasticities for all asset categories, except for time deposits. Currency is considered to be mainly a substitute for other asset classes. With regards to income effects the authors find that shares have a comparatively high volatility while the income sensitivity for mutual funds is low. The demographic variables in the FAIDS model have only a limited impact on the wealth structure. Ramb/Scharnagl found some evidence for a positive correlation between the shares of the elderly and the asset class of shares and mutual funds. Last but not least they found a positive relationship between the share of the employed and the asset class of time and debt deposits, and a negative relationship between saving deposits and shares.

Aside the broad literature dealing with the applications of AIDS and FAIDS, in the context of insurances, there is also a wide range of literature with regards to the characteristics of insurance demand. In the financial context it is common to focus on the life insurance demand. For an overview see Linderkamp (2015).

The approach of the present paper follows relatively close to Ramb/Scharnagl. We estimate a FAIDS without choosing the equation for insurance and pension entitlements as the residual equation[4], like Ramb/Scharnagl, because the focus of our paper lies on the insurance asset class. Instead we choose time deposits as our residual equation. Moreover, we complete the data at the current edge to cover the periods of the Financial- and the following European sovereign debt crisis.

3 Data and methods

We used the dataset of the Deutsche Bundesbank to cover the development of the asset structure of private Households in Germany going back to 1959.[5] We then built eight asset classes: cash and overnight deposits, time deposits, saving deposits,

[4] A residual equation is necessary in a FAIDS framework, see in particular chap. 3.

[5] Like Ramb and Scharnagl (2011). All data is broken down according to the European System of National and Regional Accounts (ESA) '95, see Ramb and Scharnagl (2011, p. 15). For a description of the asset classes according to ESA 95 see Deutsche Bundesbank (2004) and (2008).

saving bonds, bonds, shares, mutual funds and insurance and pension entitlements. The division on saving deposits and saving bonds, in contrast to the asset class "savings" in Ramb and Scharnagl (2011), has been made on the basis of the volume of both asset classes. Due to the limited availability of the corresponding return proxies for each asset class, our investigation period goes from Q1 1975 to Q1 2014[6], whereby we considered quarterly data.

The return proxies for our chosen eight asset classes also come from Deutsche Bundesbank, except for the return proxy for insurance. One problem is the consistency of the appropriate time series, due to data limitations. Therefore our main concern was to build consistent time series. For the asset class, cash and overnight deposits, we chose the monthly Frankfurt Interbank overnight rate (FIBOR) and converted it to quarter data.[7] For this study FIBOR is only available from our starting point to May 2012, for this reason we matched the FIBOR with the Euro Over Night Index Average (EONIA) rate by regressing the EONIA rate on the FIBOR. As a result we received consistent time series.[8] The proxy for time deposits returns is a weighted ratio of the return of bearer bond with a maturity of 2–3 years and a twelvemonth interest rate, because the average duration of time deposits is unknown. The weighted ratio corresponds to the ratio of bearer bond volume as proxy for time deposits with duration longer than two years and the volume of twelvemonth money as proxy for time deposits with duration of less than one year. The return of saving deposits is available from Deutsche Bundesbank and for saving bonds we chose the return of four-year bonds. Both time series ended in June 2003 and due to the lack of availability of a current suitable return proxy[9], we decided to extrapolate[10] both time series up to the current edge.

The returns of bonds are indicated by the Deutsche Rentenindex (REXP) provided by the Deutsche Bundesbank. For the period of 1975 to 1994 we received the time series of the Composite DAX (CDAX) as a proxy for the stock returns from DataStream. This data has been available from the Deutsche Bundesbank since 1994. The return of mutual funds shares is a weighted average of three sources: the constructed return of cash and overnight deposits as a proxy for the return of money market funds (available from 1994), CDAX as proxy for stock funds, and REXP as a proxy for bond investments. The ratio for the return calculation is based on the volume of these three funds.

Finally, we receive annually the straight returns ("Reinverzinsung") as a return proxy for the insurance share from Bundesanstalt für Finanzdienstleistungsaufsicht (BaFin) since 1975. The straight return is calculated as the average of the start and

[6] Due to changes from ESA 1995 to ESA 2010 in 2014 it is not possible to use the data up to the current period.

[7] To transform the data we set the start value of January, April, July and October as the corresponding quarterly data, because investments decisions of private households should be based on the current return level and not on the end value of a quarter for example.

[8] The R^2 of the regression is 0.9996.

[9] The main reason for the lack of availability is the new definition of the asset class saving deposits. The Deutsche Bundesbank states that the definitions are "only very limited comparable" (Deutsche Bundesbank 2004, p. 47).

[10] We use exponential smoothing to extrapolate the time series.

end value of one year considering only the ordinary incomes and expenses.[11] We use the annual value for each quarter value for the year in question. The mentioned return proxies are adjusted by the inflation rate[12] to receive real returns.

Additionally eight control variables are integrated to take into account the possible influences of demographics, economic and insurance specific conditions on the portfolio weights.[13] These include binary variables for the German reunification in 1991, the financial deregulation in 1994, the end of tax privilege for life insurance in 2005 and the introduction of the Riester pension scheme[14] in 2012. Moreover, the age and child dependency ratio based on the population data of the Federal Statistical Office, the unemployment rates from the Federal Employment Agency and the guaranteed interest rates from the Federal Ministry of Finance are implemented.

For our analysis we use the FAIDS model according to Blake (2004)[15]. Therefore we maximize the utility function:

$$Max\overline{U}\left(\theta_{1t} W_t, ..., \theta_{Nt} W_t\right) \tag{1}$$

under consideration of the budget constraint

$$\overline{W}_{t+1} = \sum_{i=1}^{N} \left(1 + \overline{r}_{it}\right) \theta_{it} W_t \tag{2}$$

with the following variables:

$U\ (\cdot)$ utility function
W_t real wealth at time t
θ_{it} portfolio weight of asset category i at time t
r_{it} real return on the i'th asset category at time t
N number fo asset categories in the portfolio

According to Deaton and Muellbauer (1980), who minimize the associated cost function instead of Eq. 1 and take the possible influence of the control variables Z_{jt} into account, the long run portfolio weights are defined by the following Eq. 3.

$$\theta_{it}^{*} = a_i^{*} + b_i^{*} \ln\left(W_t\left(1 + \overline{r}_{Wt}\right)\right) + \sum_{j=1}^{N} c_{ij}^{*} \ln\left(1 + \overline{r}_{jt}\right) + \sum_{j=1}^{M} h_{ij}^{*} Z_{jt} \tag{3}$$

[11] In contrast to the straight return the often used net return is calculated as the average of the start and end value of one year considering also the extraordinary incomes and expenses.

[12] Therefore the quarterly mean of the monthly one year differences in consumer price index is calculated.

[13] For a description of the control variables see Table 6 in the appendix.

[14] A Riester pension scheme is a state-promoted pension product aiming to improve the pension level in Germany. The Riester pension is supposed to compensate a reduction of the statutory pension level, which was part of the same "Riester-Reform".

[15] See Blake (2004, pp. 613–616) for the complete mathematical description of the model.

The demand theory implies some constraints for the FAIDS model which were called the adding up restrictions:

$$\sum_{i=1}^{N} a_i^* = 1; \sum_{i=1}^{N} c_{ij}^* = 0; \sum_{i=1}^{N} b_i^* = 0; \sum_{i=1}^{N} h_{ij}^* = 0 \tag{4}$$

These were implemented by leaving out one asset class during the estimation. We calculate the coefficients for the omitted asset with Eq. 4.

The theoretical assumption of homogeneity requires Eq. 5

$$\sum_{j=1}^{N} c_{ij}^* = 0 \tag{5}$$

Symmetry is imposed by Eq. 6

$$c_{ij}^* = c_{ji}^* \tag{6}$$

The different demand elasticities were calculated by the Eq. 7, 8 and 9 depending on the respective coefficients. The wealth elasticity is given by

$$\eta_{\mathrm{iWt}} = \frac{b_i^*}{\theta_{it}} + 1 \tag{7}$$

and the uncompensated interest rate elasticity by

$$e_{\mathrm{ijt}} = \frac{c_{ij}^*}{\theta_{it}} + \delta_{ij} \tag{8}$$

where δ_{it} represents the Kronecker delta.

Subject to the design of the additional variables the corresponding elasticities were derived from these equations:

$$\xi_{\mathrm{ijt}} = \frac{h_{ij}^*}{\theta_{it}} z_{jt} \quad \text{or} \quad = \frac{h_{ij}^*}{\theta_{it}} \tag{9}$$

The estimation of the coefficients for the long-run elasticities is performed using three-stage least squares on Eq. 10, where Δ_s represents the difference operator[16].

$$\begin{aligned}\theta_{it} =& a_i^* + \sum_{j=1}^{N-1} \lambda_j^* \Delta\theta_{j,t-1} + b_i^* \ln\left(W_t\left(1 + r_{Wt}\right)\right) + \sum_{j=1}^{N-1} c_{ij}^* \ln\left(1 + r_{jt}\right) \\ &+ \sum_{j=1}^{M} h_{ij}^* Z_{jt} + \sum_{s=1}^{K} b_{is}^* \Delta_s \ln\left(W_t\left(1 + r_{Wt}\right)\right) \\ &+ \sum_{s=1}^{K}\sum_{j=1}^{N-1} c_{\mathrm{ijs}}^* \Delta_s \ln\left(1 + r_{jt}\right) + \sum_{s=1}^{K}\sum_{j=1}^{M} h_{\mathrm{ijs}}^* \Delta_s Z_{jt} + u_{it}^*\end{aligned} \tag{10}$$

This equation includes the assumption of a representative agent and of rational expectations so that the expected future returns can be replaced by the contemporaneous returns. Furthermore the equation implies the endogeneity of the current values of portfolio weights, asset returns, the total wealth and the weak exogeneity of the control variables.

4 Hypotheses, results and discussion

4.1 Descriptive statistics

Insurance and pension entitlements are one of the most important asset classes in private households' portfolio in the last forty years. Fig. 1 shows the distribution of private households' wealth from 1975 to 2014.[17]

The time series shows significant changes in the portfolio structure of the private households in the period of observation. For example, the share of insurance and pension entitlements grows from 22% in 1975 to 38% in 2014. At the same time saving deposits reduces from 36 to 12%. Cash and overnight deposits increases from 10% in 2002 to 23% in 2014. The reasons for these portfolio changes are diverse. Political crisis with strong impacts on private households in Germany, for example the second oil crisis[18] in 1979, as well as the economic cycles over time should both have an impact on the interest level. Moreover, there are specific factors in Germany which might influence the portfolio distribution. Worth mentioning here is the German reunification as well as the regulatory changes, for example the abolition of the tax privilege for German life insurance policies in 2005.

[16] The difference operator is defined as $(1\text{-}L^s)$.

[17] For an overview of the asset distribution from 1959 to 2009 see Ramb and Scharnagl (2011).

[18] Probably the first oil crises in 1973 influence also the portfolio distribution in 1975.

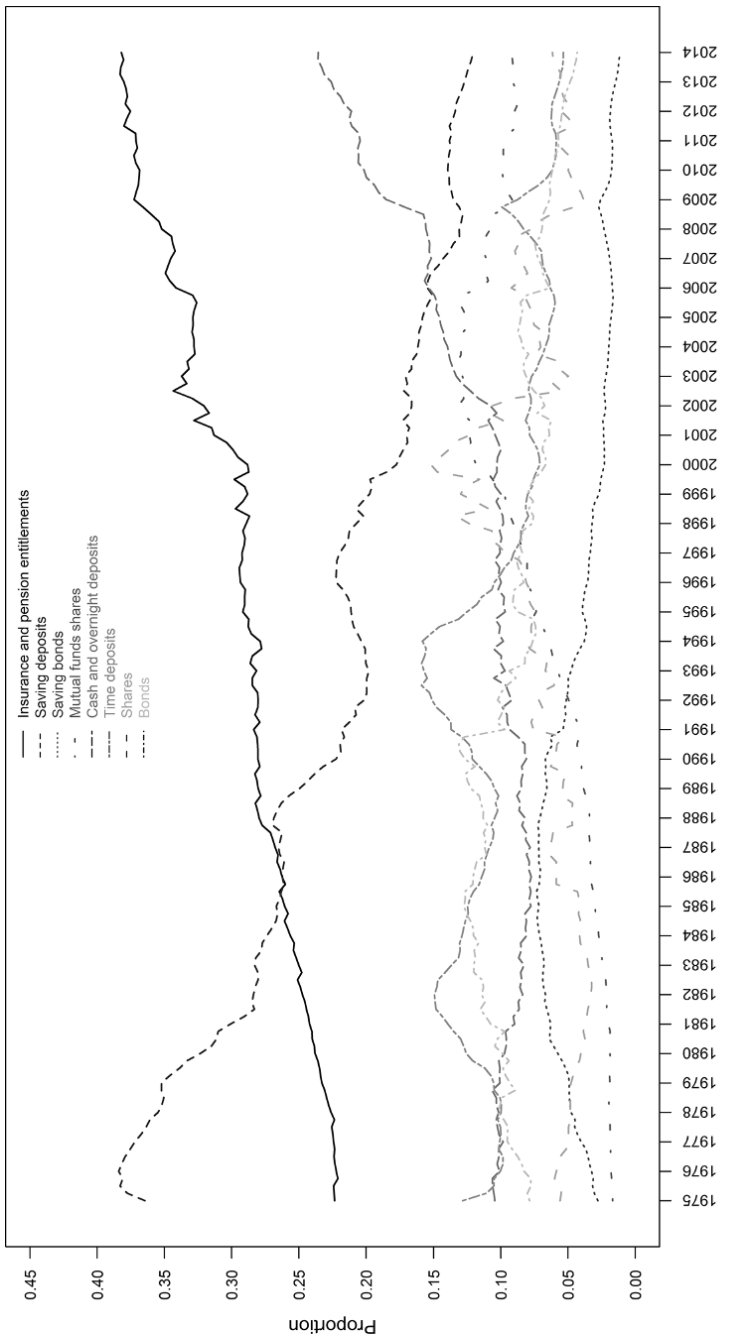

Fig. 1 Development of the asset shares over time

4.2 Hypotheses

We focused on four points: The wealth elasticity of the eight asset classes, the own-rate elasticity of the insurance share, the reaction of the insurance share to changes of the returns of the other asset classes, and finally the impact of the guaranteed interest rate as well as of other variables on the insurance share. Each aspect is expressed in the hypotheses in order to structure our analysis. Each hypothesis is motivated, analyzed, and discussed in a separate section.

H1: The wealth elasticity is expected to be at least ≥ 0.

We expect a positive reaction of the portfolio shares, if the total wealth level increases. All financial assets should be traded as normal goods.

H2: The own-rate elasticity of the insurance share is expected to be at least ≥ 0.

This hypothesis is derived directly from the neoclassical demand theory. If the relative attractiveness of an asset class increases, the demand increases too.

H3: The insurance share decreases if the rates of return of the other asset classes increase and vice versa.

Increasing returns of the other asset classes make the asset class insurance less attractive.

H4: The insurance share increases, if the guaranteed interest rate increases.

An increase of the guaranteed interest rate level leads to expectations of a higher return and therefore to a higher demand for the asset class insurance.

5 Estimation results

Table 1 provides the elasticity estimation without the restrictions of homogeneity and symmetry.[19]

5.1 Hypothesis 1

With regard to hypothesis 1 we found that the shares of equity and mutual funds react quite elastic. Insurance entitlements show nearly a proportional reaction, while bonds and saving deposits seem to be quite inelastic in regards to the changes in wealth level. Saving bonds show no significant reaction.

The wealth elasticity of the insurance share (1.0357) indicates a nearly proportional reaction on a 10% significance level in regards to the changes in wealth level. This indicates a constant relative risk aversion of the private households, if insurance and pension entitlements are seen as non-risky assets. Müller (1998) distinguish two main demand motives for insurance: security and asset accumulation. Our results

[19] The corresponding coefficients are shown in Table 5 in the appendix. In Table 5 also the calculated (according to the adding up restrictions) coefficients of our residual asset class "time deposits" are reported.

Table 1 Elasticity estimations without restrictions

	Portfolio shares						
	Insurance and Pension	Mutual funds	Saving bonds	Saving deposits	Cash	Shares	Bonds
Wealth	1.0357*	2.2984***	1.0873	0.5630***	0.7833***	2.8686***	0.1700***
Insurance_i	0.8299	–4.8728***	9.5949***	1.3954***	1.3520*	–8.9096***	3.9067***
Mutual funds_i	–0.0554	1.7066***	–0.9521***	0.0297	–0.0312	2.1377***	–0.9014***
Saving bonds_i	2.6080***	21.3314***	–11.0430***	–4.1188***	1.4276*	1.8387	–3.3858**
Saving deposits_i	–1.4466***	–21.7289***	–1.1746	6.6622***	5.5761***	–1.5995	–3.0234
Cash_i	–1.1546***	1.2086*	7.4187***	–3.5938***	–5.5587***	1.0898	6.2959***
Shares_i	–0.0077	–0.4740***	0.4031***	–0.0001	0.0434	0.4155***	0.4405***
Bonds_i	–0.0469	–0.3312	0.8284***	0.3168***	–0.7877***	–1.3290***	2.0633***
German reunification	0.0117	–0.6374***	–0.3141***	0.0615***	0.4375***	–0.9657***	–0.0196
Riester scheme	0.0250***	–0.2635***	0.6504***	0.0186	0.0631**	–1.1645***	0.3714***
Deregulation	–0.0001	0.0988**	0.0326	0.0073	–0.1436***	–0.0308	0.2401***
Tax privilege	0.0240***	–0.3136***	0.1377***	0.0249**	–0.0189	0.1794**	–0.1857***
Guaranteed interest rate	–0.0475***	0.3121***	0.2025**	0.1525***	–0.4619***	0.4978***	0.0694
Unemployment rate	0.0267**	0.5226***	–0.6702***	–0.0397**	–0.1562***	0.0765	0.2503***
Old-age dependency ratio	0.5773***	4.0631***	–5.2425***	–0.6820***	1.6712***	0.5172	–0.3103
Child dependency ratio	–0.5128***	1.7813***	–0.3066	0.2975***	–0.9825***	2.9001***	–1.3362***

Significance levels: *** ≙ 0.01; ** ≙ 0.05; * ≙ 0.10

could lead, according to Müller, to the assumption that for insurance and pension entitlements security (in the sense of financial security for relatives) could be derive as the dominant demand motive and not a return optimization.

Insurance and pension entitlements can be treated as normal goods like the other asset classes. As predicted by the economic theory neither asset class shows inferior behavior. According to our results, shares and mutual funds can be considered as superior goods. These are often used to build up wealth, which is a typical luxury concern.

5.2 Hypothesis 2

The own-rate elasticity of the insurance share is expected to be at least ≥ 0 according to the neoclassical demand theory. The estimation shows that the own-rate elasticity of the insurance share is 0.8299, but the result is not significant. The fact that the insurance return has no significant impact on the insurance share indicates that the return level is not relevant for the demand for insurances in Germany. This result supports our assumption that security could be the relevant demand motive for the asset class insurance.

5.3 Hypothesis 3

We find for saving deposits and cash the expected negative relation between the return rates of these asset classes and the insurance share. The price elasticity of saving bonds is positive (2.608), while the impact of the return of mutual funds, shares and bonds is not significant.

Following the risk-return approach of private households, negative coefficients for the returns of the other asset classes with regard to the insurance share are consistent in this framework. Therefore the positive price elasticity of saving bonds is surprising especially as the effect is significant. In addition the results show no significant correlation between the equity return and the insurance share. Therefore the asset class insurance cannot be seen as ‘safe haven’ in times of falling stock markets.

It should be noted that on the other hand the insurance return has a strong complementary effect on the shares of saving bonds (9.5949) and bonds (3.9067) and there are strong substituting effects on shares (–8.9096) and mutual funds (–4.8728). This could also indicate that on the one hand the insurance return is seen as a proxy for other security-oriented asset classes and on the other hand increasing insurance return makes risky asset classes like shares and mutual funds comparably unattractive. We assume that the demand for insurance entitlements is characterized by security considerations due to the product characteristics, while shares and mutual funds were bought to increase private households’ portfolio return.

5.4 Hypothesis 4

We cannot confirm hypothesis 4. Our results show a significant, negative relation between the guaranteed interest rate level and the share of insurance and pension entitlements (–0.0475). This result is surprising, because a higher guaranteed interest rate level will increase the attractiveness of the asset class insurance and pension entitlements. An explanation might be, that the guaranteed interest rate level is set subsequently by law. This implies that an increase of the guaranteed interest rate level takes place after periods of economic growth, which has already affected the other asset classes in a positive way and vice versa in the case of an economic downturn. Another explanation may lie in the assumption of a representative agent, as the results of e. g. Døskeland and Nordahl (2008) indicate that cumulative prospect theory is needed to explain the demand of insurance products with guarantees.

In addition to hypothesis 4, we find effects of the other additional variables. The age variables (old-age dependency ratio and child dependency ratio) lead to a positive respective negative inelastic reaction of the insurance share. Furthermore, the insurance share of private households almost shows no elastic or no significant reaction to our other additional variables.

Overall we cannot find any strong impact of the additional economic variables on the insurance and pension share. It seems that the decisions of private households about the level of their insurance investments is independent from regulatory changes; keeping in mind that the elasticities show long term effects. As the coefficients indicated, the only variable which influence the long-term insurance and pension distribution is the age structure. The higher the share of elderly is, the higher is the insurance and pension share and vice versa. The results could also be explained by the fact that the coefficient covers the whole period under consideration. This might overlap the antagonizing effect that the younger people of the current generation are quite aware of the need to build up an additional private old-age provision.[20]

Table 1 shows the elasticity estimations without any restrictions. One often asked question in the literature is whether the restrictions of homogeneity and symmetry hold or not. Homogeneity means that the underlying demand function is homogenous of degree zero in prices and income. This implies that, if all prices and incomes are multiplied by a factor k, the demand does not change. Symmetry means that the coefficients have the same impact in both directions. Both assumptions are based on the model of the homo oeconomicus. To test whether we should include the restrictions of homogeneity and symmetry, we performed a log-likelihood ratio test. The results are shown in Table 2.

The test indicates that the assumptions of homogeneity and symmetry should be rejected. Nevertheless a restricted version[21] of the FAIDS is estimated to check the robustness of the results. We find that the results do not differ much[22], but there are some implausible results in the restricted model, for example the negative own-rate

[20] See for example Linderkamp and Zuchandke (2012, p. 536).

[21] Including the restrictions of homogeneity and symmetry.

[22] The results of the restricted FAIDS are shown in Table 4 in the appendix.

Table 2 Test of the homogeneity and symmetry restrictions

	Likelihood-ratio	Chi^2 (df)
Homogeneity	39.79	14.07 (7)
Symmetry	704.57	32.67 (21)
Homogeneity and symmetry	8291.10	41.34 (28)

elasticity of the insurance share. This confirms our decision to reject the restricted FAIDS.

Naturally this study has several limitations. As mentioned above the estimated elasticities show the long-term effects for the time period of 1975 to 2014. Therefore we cannot identify short run dynamics, which could be expected in the case of regulatory changes or economic cycles. As our model is based on a representative agent and on rational expectations we cannot account for behavioral factors in private households' portfolio choice. Like previous empirical papers estimating FAIDS we cannot exclude spurious results, because not all share- and return time series are stationary[23]; but we have at least unbiased results. We treat our data like Ramb/Scharnagl did, as I(1). Another challenge is the construction of consistent return time series for such long periods under our consideration. At least some asset classes might be heterogeneous, for example mutual funds, but our model only allows us to approximate the corresponding return by only one return proxy. Furthermore we are aware that we underlie data restrictions concerning the determination of consistent and appropriate return proxies for the investment decisions of private households for each asset class.

6 Conclusion

In this paper we present a unique dataset for the wealth distribution in Germany from 1975 to 2014, whereby we consider data quarterly. Following the approach from Ramb/Scharnagl, we focus on the asset class insurance and pension entitlements and estimate FAIDS to investigate the long run elasticities of the eight asset classes under consideration.

FAIDS is estimated without the restrictions of homogeneity and symmetry, according to our test results these restrictions should be rejected. We found that the insurance and pension share reacts nearly proportional to changes in the total wealth level, while changes in the own return level have no significant impact. For that reason we derived security as the dominant demand motive for insurances and not return optimization due to the product characteristics. This could explain the continual upward trend of the asset class insurance and pension entitlements in the portfolio. It remains to be seen whether this trend also holds during and after the phase of low interest rates as a consequence of the financial crisis. This question should be addressed in further research projects. The only additional economic variable which influences the long-term insurance and pension share in private households' portfo-

[23] See Table 3 in the appendix.

lio is the age structure. We found a positive relation between the share of the elderly in Germany and the share of insurances and pensions in the portfolio. Considering that the coefficient covers the whole period from 1975 to 2014 and therefore cannot show potential opposite short run effects.

Appendix

Table 3 Descriptive statistics

	Min	Mean	Max	SD	Start-value	End-value	KPSS
Shares (%)	3.24	6.69	15.20	2.65	5.59	6.16	0.6788***
Mutual funds shares (%)	1.68	6.79	13.20	3.98	1.68	9.21	0.664***
Saving bonds (%)	1.14	4.04	7.34	2.02	2.79	1.14	0.6834***
Saving deposits (%)	12.00	22.30	38.40	7.43	36.45	12.05	0.7406***
Cash and overnight deposits (%)	7.74	11.90	23.60	4.27	10.45	23.56	1.1633***
Time deposits (%)	5.34	10.00	15.90	3.02	12.84	5.34	0.5154***
Insurance and pension entitlements (%)	22.10	29.40	38.30	4.73	22.34	38.21	0.6879***
Bonds (%)	4.32	8.83	13.10	2.23	7.86	4.32	0.5838***
Wealth (bn)	462.9	2402.0	4970.0	1387.7	462.9	4969.9	0.8658***
Insurance_i (%)	0.32	4.04	8.33	1.70	2.05	3.19	0.543***
Mutual funds_i (%)	–19.72	6.29	29.02	9.96	0.32	13.87	0.0519*
Saving bonds_i (%)	–3.06	1.96	5.98	2.31	2.18	–1.21	0.9848***
Saving deposits_i (%)	–3.02	–0.48	3.32	1.13	–0.73	–1.20	0.442***
Cash_i (%)	–2.20	1.97	6.16	1.98	1.79	–0.86	0.8158***
Shares_i (%)	–44.00	8.83	75.61	22.86	–2.81	19.63	0.0491*
Bonds_i (%)	–11.65	4.62	15.33	5.13	5.31	1.50	0.0751*
Time deposits_i (%)	–1.42	2.89	6.72	1.72	2.81	–0.63	0.7442***
Guarenteed interest rate (%)	1.75	3.09	4.00	0.61	3.00	1.75	1.1812***
Unemployment rate (%)	3.40	8.80	13.93	2.59	5.03	8.03	0.8104***
Old-age dependency ratio	23.54	27.28	34.12	3.63	25.20	34.12	1.2708***
Child dependency ratio	29.68	36.55	51.00	6.11	51.00	29.68	1.0583***

Significance levels: *** ≙ 0.01; ** ≙ 0.05; * ≙ 0.10

Table 4 Elasticity estimations with restriction of homogeneity and symmetry

Return rates and control variables	Portfolio shares						
	Insurance and pension	Mutual funds	Saving bonds	Saving deposits	Cash	Shares	Bonds
Wealth	1.0162	2.0467	1.2992	0.5199	0.7212	22.079	0.6082
Shares_i	–0.0509	0.2076	–0.1605	–0.0947	–0.1948	11.869	0.4439
Mutual funds_i	0.0184	–0.5016	0.5984	0.2773	0.7390	0.2108	–1.0338
Saving bonds_i	1.1987	0.3563	–2.8083	–3.6118	4.6524	–0.0970	0.3805
Saving deposits_i	0.1063	0.9098	–19.9068	5.6302	–3.2919	–0.3154	1.0542
Cash_i	–0.0044	1.2955	13.6999	–1.7588	–1.0659	–0.3468	0.2389
Insurance_i	–0.1172	0.0799	8.7293	0.1404	–0.0108	–0.2242	–0.5084
Bonds_i	–0.1525	–1.3441	0.8309	0.4177	0.1772	0.5860	0.4248
German reunification	0.0000	–0.0119	–0.8977	–0.0061	0.1680	–0.4201	–0.0679
Riester scheme	–0.0265	–0.1678	0.4130	–0.0615	–0.0632	–0.9298	0.3397
Deregulation	0.0441	–0.1752	0.4328	0.1041	0.1268	–0.2227	0.0132
Tax privilege	0.0049	–0.5035	0.1358	0.0046	–0.0694	0.0176	0.0215
Guaranteed interest rate	–0.1192	–0.3092	0.3413	0.1225	–0.3418	0.4963	0.1438
Unemployment rate	0.0225	0.6684	–0.8977	–0.0485	–0.2570	0.3618	0.2401
Old–age dependency ratio	0.5433	2.0021	–3.9814	–0.3302	2.7125	18.238	–1.4381
Child ratio	–0.5535	2.2524	–0.6949	0.1054	–1.5452	21.377	–0.5243

Table 5 Coefficients of the elasticity model (p-values in brackets) without restrictions of homogeneity and symmetry

Return rates and control variables	Portfolio shares							
	Insurance and Pension	Mutual funds	Saving bonds	Saving deposits	Cash	Shares	Bonds	Time deposits
Wealth	0.0105 (0.051)	0.0882 (< 0.001)	0.0035 (0.527)	–0.0974 (< 0.001)	–0.0258 (0.002)	0.1250 (< 0.001)	–0.0733 (< 0.001)	0.0105
Insurance_i	–0.0501 (0.413)	–0.3310 (< 0.001)	0.3880 (< 0.001)	0.3110 (< 0.001)	0.1610 (0.090)	–0.5960 (< 0.001)	0.3450 (0.008)	–0.0501
Mutual funds_i	–0.0163 (0.120)	0.0480 (0.001)	–0.0385 (< 0.001)	0.0066 (0.595)	–0.0037 (0.820)	0.1430 (< 0.001)	–0.0796 (< 0.001)	–0.0163
Saving bonds_i	0.7680 (< 0.001)	1.4490 (< 0.001)	–0.4870 (< 0.001)	–0.9180 (< 0.001)	0.1700 (0.090)	0.1230 (0.462)	–0.2990 (0.028)	0.7680
Saving deposits_i	–0.4260 (0.001)	–1.4760 (< 0.001)	–0.0475 (0.722)	1.2620 (< 0.001)	0.6640 (0.001)	–0.1070 (0.751)	–0.2670 (0.329)	–0.4260
Cash_i	–0.3400 (< 0.001)	0.0821 (0.075)	0.3000 (< 0.001)	–0.8010 (< 0.001)	–0.7810 (< 0.001)	0.0729 (0.383)	0.5560 (< 0.001)	–0.3400
Shares_i	–0.0023 (0.562)	–0.0322 (< 0.001)	0.0163 (< 0.001)	0.0000 (0.996)	0.0052 (0.393)	–0.0391 (< 0.001)	0.0389 (< 0.001)	–0.0023
Bonds_i	–0.0138 (0.271)	–0.0225 (0.211)	0.0335 (0.010)	0.0706 (< 0.001)	–0.0938 (< 0.001)	–0.0889 (0.006)	0.0939 (< 0.001)	–0.0138
German reunification	0.0034 (0.280)	–0.0433 (< 0.001)	–0.0127 (< 0.001)	0.0137 (< 0.001)	0.0521 (< 0.001)	–0.0646 (< 0.001)	–0.0017 (0.797)	0.0034
Riester scheme	0.0074 (0.002)	–0.0179 (< 0.001)	0.0263 (< 0.001)	0.0042 (0.138)	0.0075 (0.040)	–0.0779 (< 0.001)	0.0328 (< 0.001)	0.0074
Deregulation	0.0000 (0.993)	0.0067 (0.036)	0.0013 (0.565)	0.0016 (0.537)	–0.0171 (< 0.001)	–0.0021 (0.721)	0.0212 (< 0.001)	0.0000
Tax privilege	0.0071 (< 0.001)	–0.0213 (< 0.001)	0.0056 (0.006)	0.0056 (0.017)	–0.0023 (0.459)	0.0120 (0.018)	–0.0164 (< 0.001)	0.0071
Guaranteed interest rate	–0.0140 (< 0.001)	0.0212 (< 0.001)	0.0082 (0.045)	0.0340 (< 0.001)	–0.0550 (< 0.001)	0.0333 (0.001)	0.0061 (0.465)	–0.0140

Table 5 (Continued)

Return rates and control variables	Portfolio shares							
	Insurance and Pension	Mutual funds	Saving bonds	Saving deposits	Cash	Shares	Bonds	Time deposits
Unemployment rate	0.0079 (0.012)	0.0355 (< 0.001)	–0.0271 (< 0.001)	–0.0088 (0.017)	–0.0186 (< 0.001)	0.0051 (0.528)	0.0221 (0.001)	0.0079
Old-age dependency ratio	0.1700 (< 0.001)	0.2760 (< 0.001)	–0.2120 (< 0.001)	–0.1520 (< 0.001)	0.1990 (< 0.001)	0.0346 (0.484)	–0.0274 (0.497)	0.1700
Child dependency ratio	–0.1510 (< 0.001)	0.1210 (< 0.001)	–0.0124 (0.276)	0.0663 (< 0.001)	–0.1170 (< 0.001)	0.1940 (< 0.001)	–0.1180 (< 0.001)	–0.1510

Table 6 Description of the control variables

Control variables	
Variable	Description
German reunification	Dummy variable: 0 if year < 1991; 1 if year > 1991
Riester scheme (Introduction of the Riester pension scheme)	Dummy variable: 0 if year < 2002; 1 if year > 2002
Deregulation (financial deregulation of the German insurance market)	Dummy variable: 0 if year < 1994; 1 if year > 1994
Tax privilege (End of the tax privilege for life insurances in Germany)	Dummy variable: 0 if year < 2012; 1 if year > 2012
Guaranteed interest rate	Discrete variable: Q1 1975–Q2 1986: 3.00% Q3 1986–Q2 1994: 3.50% Q3 1994–Q2 2000: 4.00% Q3 2000–Q4 2003: 3.25% Q1 2004–Q4 2006: 2.75% Q1 2007–Q4 2011: 2.25% Q1 2012–Q1 2014: 1.75%
Unemployment rate	Discrete variable from the Federal Employment Agency
Child dependency ratio	Discrete variable, defined as $\frac{\text{Population under 20 years}}{\text{Population between 20 and 64 years}}$
Old-age dependency ratio	Discrete variable, defined as $\frac{\text{Population over 64 years}}{\text{Population between 20 and 64 years}}$

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