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Inzidenz von mit Diabetes assoziierten Komplikationen bei Personen mit und ohne Diabetes

Schriftliche Habilitationsleistung zur Erlangung der Venia Legendi
für das Fach Versorgungsforschung an der
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Inhaltsverzeichnis

Zusammenfassung

Die vorliegende Schrift umfasst sechs Originalarbeiten, deren übergeordnete Aufgabenstellung dahin besteht, den zeitlichen Trend der Inzidenzrate von mit Diabetes assoziierten Komplikationen bei Menschen mit und ohne Diabetes zu untersuchen. Dabei lag der Fokus der Arbeiten auf den Endstadien der Komplikationen wie Erblindung, Schlaganfall, Herzinfarkt, Amputation sowie terminale Niereninsuffizienz. Die hier vorliegenden Arbeiten analysierten, ob die alters- und geschlechtsstandardisierte Inzidenzrate in der Bevölkerung mit Diabetes gemäß einer Forderung vieler Fachleute bei einer im italienischen St. Vincent im Jahr 1989 stattgefundenen Versammlung zurückgegangen ist.

Die hier vorgestellten Originalarbeiten basieren auf etablierten populationsbezogenen epidemiologischen Methoden, beinhalten gegenüber vorliegenden Arbeiten jedoch bedeutsame methodische Erweiterungen. Dies sind vor allem die Nutzung von Krankenkassendaten oder populationsbezogenen Registerdaten mit längeren Beobachtungszeiträumen und größeren Kollektiven, eine valide Schätzung der Diabetesprävalenz, eine vollständige Erfassung aller untersuchten mit Diabetes assoziierten Komplikationen und altersadjustierte Inzidenzschätzungen.

Insgesamt stützen die Ergebnisse der Arbeiten die Annahme, dass eine Reduktion der Inzidenzraten aller o.g. Komplikationen bei Menschen mit Diabetes in stärkerem Ausmaß als bei Menschen ohne Diabetes stattgefunden hat. Die Ergebnisse zeigen aber auch, dass Menschen mit Diabetes immer noch ein höheres Risiko für jede dieser Komplikationen haben als Menschen ohne Diabetes. Die Resultate tragen zu einem besseren Verständnis bei, wie die Versorgungslage bei Menschen mit Diabetes sich entwickelt hat und welche Anstrengungen noch unternommen werden müssen, um den in St. Vincent formulierten Zielsetzungen zu genügen.

Auflistung der zugrundeliegenden Originalarbeiten

1. **Claessen H**, Kvitkina T, Narres M, Trautner C, Zöllner I, Icks A (2018): Decreasing incidence of blindness in people with and without diabetes in southern Germany, 2008–2012. Diabetes Care 41(3):478-484. (IF 15.270)

2. **Claessen H**, Narres M, Kvitkina T, Koch M, Icks A (2020): Incidence and relative risk of renal replacement therapy in people with and without diabetes between 2002 and 2016 in a German region. Diabetologia 63(3):648-658. (IF 10.122)

3. Narres M, **Claessen H***, Kvitkina T, Wilk A, Friedel H, Günster C, Hoffmann F, Koch M, Icks A (2020): Renal replacement therapy in people with and without diabetes in Germany, 2010–2016: an analysis of more than 25 million inhabitants. Diabetes Care 44(6):1291-1299. (IF 17.151)

4. Icks A*, **Claessen H***, Kvitkina T, Narres M, Weingärtner M, Schwab S, Kolominsky-Rabas PL (2017): Decreasing incidence of stroke in diabetic but not in the non-diabetic population: A community-based stroke register. PLoS One. 16; 12(11). (IF 2.766)

5. **Claessen H**, Narres M, Haastert B, Arend W, Hoffmann F, Morbach S, Rümenapf G, Kvitkina T, Friedel H, Günster C, Schubert I, Ullrich W, Westerhoff B, Wilk A, Icks A (2018): A.Lower-extremity amputations in people with and without diabetes in Germany, 2008–2012—an analysis of more than 30 million inhabitants. Clinical Epidemiology. 10:475-488. (IF 4.650)

6. **Claessen H**, Avalosse H, Guillaume J, Narres M, Kvitkina T, Arend W, Morbach S, Lauwers P, Nobels F, Boly J, Van Hul C, Doggen K, Dumont I, Felix P, van Acker K, Icks A (2018). Decreasing rates of lower-extremity amputation in people with and without diabetes in Belgium: a nationwide study. Diabetologia. 61 (9): 1966-1977. (IF 7.113)

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1 Einleitung

Weltweit sind etwa 537 Mio. Menschen zwischen 18-99 Jahren an Diabetes mellitus erkrankt mit immer noch steigender Prävalenz [IDF Diabetesatlas 2021]. Trotz Verbesserung der Früherkennung und Einsatz von modernen individualisierten Therapiestrategien geht Diabetes mellitus nach wie vor häufig mit Schädigungen der Nerven (Neuropathie) und der Gefäße (Angiopathie) einher, die u.a. die Augen (Retinopathie) und Nieren (Nephropathie) betreffen. Folgen können Erblindung, terminales Nierenversagen, Amputation, Herzinfarkt und Schlaganfall sein. Darüber hinaus weisen betroffene Personen eine deutlich eingeschränkte Lebensqualität und erhöhte Sterblichkeit auf. So wird geschätzt, dass im Jahr 2021 ca. 6,7 Millionen Menschen weltweit bzw. 1,1 Millionen in Europa an den o.g. mit Diabetes assoziierten Komplikationen gestorben sind [IDF Diabetesatlas 2021]. Daneben wird angenommen, dass diese Zahlen in den letzten beiden Dekaden weiter zugenommen haben [Global Burden of Disease Collaborative Network 2020] und die Lebenserwartung bei Personen mit Diabetes etwa 5 bis 6 Jahre kürzer ist als bei Menschen ohne Diabetes [Rao Kondapally Seshasai et al. 2011]. Weiterhin wird geschätzt, dass im Jahr 2021 insgesamt 966 Milliarden US Dollar an Gesundheitskosten aufgrund von Diabetes entstanden sind mit weiter steigender Tendenz [IDF Diabetesatlas 2021]. In Deutschland wurde geschätzt, dass etwa zwei Drittel dieser Kosten der Behandlung von mit Diabetes assoziierten Komplikationen zuzuschreiben ist [von Ferber et al. 2007].

St. Vincent Deklaration

Es wurde bereits in den 1980er Jahren aufgrund der zunehmenden Diabetesprävalenz deutlich, dass eine Reduktion von mit Diabetes assoziierten Komplikationen bei Personen mit Diabetes angestrebt werden muss. So trafen sich im Jahre 1989 auf Initiative der Weltgesundheitsorganisation (WHO) und der Europa-Sektion der International Diabetes Federation (IDF) Repräsentanten von Patientenorganisationen und Gesundheitsministerien aus allen europäischen Ländern im italienischen St. Vincent. Dabei wurden gemeinsam mit Diabetesexperten (Wissenschaftler, Ärzte etc.) sowie Vertretern von Krankenversicherungen

und Industrie Möglichkeiten zwecks Verbesserung der Diabetestherapie in Europa erörtert. Bei dieser Versammlung sind eine Reihe von Zielen zur Verbesserung der Gesundheitsversorgung für Diabetespatienten formuliert worden. [The Saint Vincent Declaration 1990]. Dabei wurden Ziele für die nächsten 5 Jahre formuliert.

Ein zentrales Ziel war zum einen die Reduktion der mit Diabetes assoziierten Komplikationen:

- Verminderung der Erblindungen aufgrund von Diabetes um ein Drittel
- Reduktion der Häufigkeit von diabetesbedingtem chronischen terminalen Nierenversagen um ein Drittel
- Senkung der Zahl von diabetesbedingten Amputationen um die Hälfte
- Reduktion von kardiovaskulären Erkrankungen wie Herzinfarkt und Schlaganfällen

Des Weiteren sollten Schwangerschaften bei Frauen mit Diabetes ähnlich wie bei Frauen ohne Diabetes verlaufen.

Die St. Vincent Deklaration führte dazu, dass in den darauffolgenden Jahren in den meisten europäischen Ländern Maßnahmen zwecks besserer Prävention und Behandlung des Diabetes mellitus getroffen wurden. So wurden strukturierte Schulungen (Selfmanagement-Trainings) für PatientInnen entwickelt und eingeführt. In Deutschland definierten nationale Versorgungsleitlinien sowie Leitlinien der Fachgesellschaft (Deutsche Diabetes-Gesellschaft, DDG) praxisrelevante Empfehlungen und Qualitätskriterien zur Diagnostik, Klassifikation, Prophylaxe, Therapie und Langzeitbetreuung des Diabetes und seiner Begleit- und Folgeerkrankungen (Bundesärztekammer 2021, Schleicher et al. 2022, Landgraf et al. 2022). In den 2000er Jahren fand die Einrichtung von Disease Management Programmen (DMP) mit dem Ziel einer strukturierten Versorgung für Menschen mit Typ 1 und Typ-2-Diabetes statt. Dazu wurden alle Möglichkeiten der modernen Kommunikation verwendet wie Informationsbroschüren, telefonische Beratungsgespräche, Erinnerungen an notwendige Arztbesuche per Telefon, Briefe, E-Mail oder SMS sowie Schulungen und Unterstützung durch telemedizinische Geräte. Ferner entwickelten sich medikamentöse und technische Behandlungsmöglichkeiten weiter.

In den 1990er Jahren wurde begonnen, die Häufigkeit aller mit Diabetes assoziierten Komplikationen mittels bevölkerungsbasierter Studien zu untersuchen. Dabei interessierten insbesondere Inzidenzraten als Zielgröße, da sie anders als bei der Prävalenz Neuerkrankungen berücksichtigen und somit die Dynamik der Erkrankungen über einen längeren Zeitraum besser erfassen. Allerdings war in den meisten Studien der Beobachtungszeitraum zu kurz, um einen zeitlichen Trend der Inzidenzraten zu untersuchen. Weiterhin nahmen viele Studien entweder keine oder keine valide Schätzung der Diabetes Prävalenz in der Bevölkerung vor, was für eine aussagekräftige Schätzung der Inzidenz in der Bevölkerung mit Diabetes notwendig ist. Ebenso wurden oft nicht alle mit Diabetes assoziierten Komplikationen vollständig erfasst oder es war nicht möglich, das erste Ereignis zu zählen. Darüber hinaus war die Studienpopulation oft zu klein um repräsentative Aussagen für die Allgemeinbevölkerung zu treffen oder es wurde versäumt, die Inzidenzraten nach Alter und Geschlecht zu adjustieren.

Aus methodischer Sicht waren somit Studien erforderlich mit einem längeren Beobachtungszeitrum, einer validen Schätzung der Diabetesprävalenz, einer vollständigen Erfassung der Ereignisse in einem größeren und repräsentativeren Kollektiv und einer nach Alter und Geschlecht standardisierten Inzidenzrate – verbunden mit der Notwendigkeit der Erschließung neuer Datenquellen und der Entwicklung von verbesserten methodischen Ansätzen.

Im nächsten Kapitel dieser Arbeit wird ein Überblick über den aktuellen Stand der Forschung bezüglich Inzidenz der mit Diabetes assoziierten Komplikationen bei Personen mit und ohne Diabetes gegeben. Entsprechend der St. Vincent Deklaration werden dabei die Endstadien der Komplikationen berichtet, als da sind: Erblindung, Schlaganfall, Nierenersatztherapie (RRT) als Marker für terminale Niereninsuffizienz, Amputation der unteren Extremitäten sowie Herzinfarkt. Anschließend wird der aus den Limitationen bisheriger Studien resultierende Forschungsbedarf erläutert. Im darauffolgenden Kapitel werden die Formulierung der Forschungsfragen für diese Arbeit und methodische Erneuerungen vorgestellt, welche für die

Schließung der Forschungslücken erforderlich waren. Im darauf anschließenden Kapitel werden die eigenen Originalarbeiten kurz vorgestellt hinsichtlich der wichtigsten Ergebnisse. Das letzte Kapitel ist eine Diskussion, inwieweit die eingangs aufgeführten St. Vincent Ziele erfüllt und Forschungslücken geschlossen werden konnten. Schlussendlich erfolgt ein abschließendes Fazit.

2 Hintergrund und Forschungsstand

2.1 Forschungsstand

Die St. Vincent Deklaration war Anlass mit Hilfe epidemiologischer Studien zu untersuchen, ob die Situation bei Personen mit Diabetes sich in den darauffolgenden Dekaden in Europa tatsächlich verbessert hat. So haben viele Studien die zeitliche Entwicklung der Inzidenz von Schlaganfall, Erblindung, RRT, Amputation und Herzinfarkt insbesondere bei Personen mit Diabetes untersucht. Nachteilig war, dass es häufig nicht möglich war die Diabetesprävalenz in der Bevölkerung zu schätzen und deswegen die Inzidenzrate bei Personen mit Diabetes lediglich auf die Gesamtpopulation bezogen wurde. Auf solche Studien wird in diesem Kapitel nicht weiter eingegangen. Darüber hinaus wird über Studien, die keinen Vergleich mit der Bevölkerung ohne Diabetes vorgenommen haben, hier nicht weiter berichtet, da die Entwicklung vergleichend sowohl in diabetischer wie in nichtdiabetischer Population betrachtet werden soll. Dies ist in der St. Vincent Deklaration nicht explizit benannt, erscheint jedoch sinnvoll: Die dort formulierten Ziele sollten Ergebnisse einer verbesserten Diabetes-Versorgung sein, während Veränderungen von Inzidenzen auch andere Ursachen haben können.

Erblindung

In Deutschland fand erstmals die Untersuchung der Erblindungsinzidenz bei Personen mit und ohne Diabetes zwischen 1990 und 1998 statt [Trautner et cal 2001]. Studienregion war Württemberg-Hohenzollern, eine Region in Baden-Württemberg mit etwa 5,4 Millionen

Einwohnern. Es zeigte sich, dass die Erblindungsinzidenz bei Personen mit Diabetes signifikant um etwa 3 Prozent (95% Konfidenzintervall (KI): 1% - 5%) pro Jahr gesunken war (1990: 72 pro 100.000 Personenjahre (PJ), 1998: 59 pro 100.000 PY) während bei Personen ohne Diabetes keine Veränderung zu erkennen war (1990: 36 pro 100.000 PJ, 1998: 38 pro 100.000 PY). Die Erblindungsinzidenz war bei Menschen mit Diabetes im Durchschnitt signifikant höher verglichen mit Personen ohne Diabetes (relatives Risiko: 5,2; 95% KI: 4,2 – 6,4). Außerhalb Deutschlands gibt es nach besten Wissen des Verfassers bislang keine bevölkerungsbezogene Studie, welche die Erblindungsinzidenz bei Personen mit und ohne Diabetes untersucht hat. Zudem ist selbst die Anzahl an internationalen Studien, welche die Inzidenzrate innerhalb der Population mit Diabetes über einen längeren Zeitraum untersucht haben, ziemlich limitiert. So fand eine Untersuchung der Erblindungsinzidenz in den 1990er und 2000er Jahren in der polnischen Region Ermland-Masuren (ca. 1,4 Millionen Einwohner) sowie in der schottischen Council Area Fife (ca. 360.000 Einwohner) mit Hilfe von bevölkerungsbezogenen Blindenregistern statt [Bandurska-Stankiewicz et al. 2006, Hall et al. 2013]. Die Erblindungsinzidenz in Polen sank von 102,4 pro 100.000 PJ in 1989 auf 13,3 in 2004, während in Schottland dieser Rückgang etwas moderater ausfiel (64,3 pro 100.000 PJ in 1990-1999; 42,7 in 2000-2009).

Die Aussagekraft der Ergebnisse hinsichtlich Erreichung der St. Vincent Ziele war in diesen Studien jedoch eingeschränkt. So konnte in einer deutschen Studie bei der Schätzung der Bevölkerung mit Diabetes durch das Diabetesregister Ost-Berlin 1988 weder eine für die Region noch für den Beobachtungszeitraum repräsentative Diabetesprävalenz geschätzt werden. Darüber hinaus blieb unklar, welchen Einfluss eine zeitliche Veränderung der Diabetesprävalenz auf den zeitlichen Trend gehabt hätte. Eine weitere Limitation dieser Studien war, dass der Alterseffekt bei der Untersuchung der Inzidenzraten unberücksichtigt blieb, so dass nicht auszuschließen ist, dass die Ergebnisse durch eine heterogene Altersverteilung verzerrt waren. Die Studie aus Schottland verwendete darüber hinaus eine deutlich weniger strenge Definition der Erblindung, so dass die Inzidenzraten per se erheblich höher und somit schwerer mit den deutschen Studien vergleichbar waren. Im Gegensatz dazu

war die Anzahl an beobachteten Erblindungen in der Studie aus Polen so gering (30 Erblindungen in 1989, 6 in 2014), dass die Aussagekraft trotz des deutlichen absoluten Rückgangs nur eingeschränkt ist.

Schlaganfall

In Deutschland fand eine Analyse der Schlaganfallinzidenz zwischen dem 1.1.2005 und 31.12.2007 bei allen Versicherten der Gmünder Ersatzkasse (GEK), einem Kollektiv von etwa 1,6 Millionen Personen, statt [Icks et al 2011]. Die Schlaganfallinzidenz lag bei Männern mit Diabetes bei 476 pro 100.000 PJ (95% KI: 438-514) und war etwa doppelt so hoch im Vergleich zu Männern ohne Diabetes (255 pro 100.000 PJ (243-266)). Bei Frauen war das Verhältnis ähnlich, wobei die Schlaganfallinzidenz insgesamt etwas niedriger lag (Frauen mit Diabetes: 342 pro 100.000 PJ (305-378). Frauen ohne Diabetes: 173 pro 100.000 PJ (163-186). Das Personen mit und ohne Diabetes vergleichende relative Risiko lag bei Männern und Frauen bei 1,9 (95% KI 1,7-2,0) bzw. 2,0 (1,8-2,2). Daraus folgt, dass Menschen mit Diabetes signifikant häufiger einen Schlaganfall erlitten.

Aufgrund des relativ kurzen Beobachtungszeitraumes war es bei dieser Studie nicht möglich, die zeitliche Entwicklung der Schlaganfallinzidenz zu untersuchen. Weiterhin war es in dieser Studie nicht möglich den ersten Schlaganfall pro Person zu erfassen. Es wurde zwar nur erste Schlaganfälle gezählt von Personen, die im Vorjahr 2004 keinen Schlaganfall hatten (ein Jahr „Wash-Out“). Allerdings war eine Überschätzung der Inzidenzrate nicht auszuschließen, da solche Personen fälschlicherweise mitgezählt wurden, wenn sie vor dem Jahr 2004 einen Schlaganfall erlitten haben.

International gibt es eine Reihe von bevölkerungsbezogenen Studien mit Berücksichtigung der Diabetesprävalenz und Untersuchung der Inzidenzrate in der Bevölkerung mit und ohne Diabetes [Bragg et al. 2016, Mulnier et al. 2006, Schableger et al. 2015, Price et al. 2018, Lopez-De Andres et al. 2021, Peters et al. 2020, Folsom et al. 1999, Hu et al. 2002, Janghorbani et al. 1994, Khoury et al. 2013, Malla et al 2019, Liao et al 2015, Kim et al 2021, Davis et al 2020]. Die Schlaganfallinzidenz, wo alle Schlaganfälle (fatale sowie nicht-fatale)

beliebiger Ursache gezählt wurden, variierte bei Personen mit Diabetes zwischen 402 pro 100,000 PJ in Deutschland in den 2000er Jahren [Icks et al. 2011] und 1.191 in den 1990er Jahren im Vereinten Königreich [Mulnier et al. 2006]. Das die Bevölkerungen mit und ohne Diabetes vergleichende relative Risiko variierte zwischen 1,0 und 2,84.

Die Hauptlimitation dieser Studien war jedoch, dass ihr Beobachtungszeitraum zu kurz war und so kein zeitlicher Trend der Inzidenzraten untersucht werden konnte. Es gibt nach besten Wissen des Verfassers bisher lediglich drei bevölkerungsbasierte Studien, welche den zeitlichen Trend der Schlaganfallinzidenz in der Bevölkerung mit und ohne Diabetes untersucht haben unter Berücksichtigung der Diabetesprävalenz [Rautio et al. 2008, Munoz-Rivas et al 2016, Read et al 2018].

In den nordschwedischen Provinzen Norrbotten und Västerbotten (ca. 500.000 Einwohner) fand die Untersuchung der Schlaganfallinzidenz in der Population mit und ohne Diabetes mit Hilfe eines MONICA Schlaganfallregisters statt, wo systematisch alle ersten sowie darauffolgenden Schlaganfälle erfasst werden [Rautio et al. 2008]. Dabei wurde im Zeitraum 1985 - 2003 ein nach Alter adjustierter signifikanter Rückgang der Schlaganfallinzidenz bei Frauen mit Diabetes (1,5% pro Jahr (95% KI 0,3%-2,7%) sowie Männern ohne Diabetes (0,8% (0,3%-1,3%)) beobachtet, während diese Zahl bei Männern mit Diabetes und Frauen ohne Diabetes nahezu konstant blieb. In Spanien wurde ebenfalls der zeitliche Trend untersucht mit einem Schlaganfallregister, wo kontinuierlich alle hämorrhagischen Schlaganfälle gezählt wurden [Munoz-Rivas et al. 2016]. Anders als in Schweden blieb die Inzidenzrate des hämorrhagischen Schlaganfalls in Spanien zwischen 2003 und 2012 in allen Subgruppen nahezu stabil. Die dritte Studie mit Untersuchung des zeitlichen Trends bei Personen mit und ohne Diabetes war eine retrospektive Kohortenstudie mit Verlinkung von Krankenhausentlassungsdaten in Schottland, welche die Inzidenzrate von ischämischem Schlaganfall zwischen 2004 und 2013 untersuchte [Read et al. 2018]. Die Inzidenzrate sank in beiden Populationen mit und ohne Diabetes in einem ähnlichen Ausmaß signifikant um 2,7 Prozent pro Jahr (95% KI 2,4%-3,0%). Beim Vergleich von Menschen mit und ohne Diabetes

war In Schweden die Schlaganfallinzidenz mit Faktor 5 bis 8 überraschend viel höher bei Personen mit Diabetes im Vergleich zu Personen ohne Diabetes. Dagegen war dieser Unterschied bei den hämorrhagischen Schlaganfällen in Spanien mit einem relativen Risiko von 3,3 und den ischämischen Schlaganfällen in Schottland mit relativen Risiken von 1,23 (Männer) bzw. 1,41 (Frauen) auf einem ähnlichen Niveau wie in der deutschen Studie. Die Unterschiede zwischen diabetischer und nichtdiabetischer Population waren überall signifikant.

Die Aussagekraft der Studienergebnisse bezüglich der Erreichung der St. Vincent Ziele war jedoch eingeschränkt. So wurden in Spanien nur hämorrhagische Schlaganfälle gezählt (ca. 15% aller Schlaganfälle). Eine weitere Limitation der spanischen Studie war, dass der Alterseffekt bei der Schätzung der Inzidenzraten anders als in Deutschland nicht berücksichtigt wurde. In der schwedischen Studie war dagegen die Studienpopulation auf Personen zwischen 35 und 74 Jahre begrenzt. Bei der schottischen Studie ist die Adjustierung nach Alter zwar berücksichtigt worden, allerdings gingen nur ischämische Schlaganfälle in die Auswertung ein, was die Vergleichbarkeit zu den anderen Studien erschwert.

Terminale Niereninsuffizienz/RRT

In Deutschland fanden Untersuchungen der Inzidenzrate der terminalen Niereninsuffizienz – operationalisiert über eine beginnende RRT – in der Bevölkerung mit und ohne Diabetes erst ab den 2000er Jahren statt. Eine Studie analysierte im Zeitraum 2002 bis 2008 alle Personen ab 30 Jahren mit erstmaliger RRT anhand der Daten aus dem Dialysezentrum Mettmann, welches als einziges Behandlungszentrum systematisch nahezu alle RRT-Fälle in der Region um Düsseldorf (Kreis Mettmann ohne Monheim, Langenfeld und Ratingen) erfasst [Icks et al. 2010]. Die Inzidenzrate lag bei Männern und Frauen mit Diabetes bei 213,7 bzw. 159,5 pro 100.000 PJ, während sie bei Männern und Frauen ohne Diabetes bei 26,9 bzw. 16,4 pro 100.000 PJ lag. Somit war das Personen mit und ohne Diabetes vergleichende relative Risiko bei Männern und Frauen etwa 7,9 (95% KI: 5,9 -10,8) bzw. 8,0 (4,7-13,5), so dass Menschen mit Diabetes unabhängig vom Geschlecht signifikant häufiger betroffen waren.

Parallel dazu untersuchte eine Studie die RRT-Inzidenzrate für den Zeitraum 1.4.2006 - 7.10.2008 innerhalb des Versichertenkollektivs der Gmündner Ersatzkasse (GEK, ca. 1,6 Millionen Personen) [Hoffmann et al. 2011] für alle Menschen ab 30 Jahren. Es zeigte sich, dass die Inzidenzraten von der Größenordnung her ähnlich hoch waren wie jene der Studie aus Mettmann (Männer und Frauen mit Diabetes: 186,6 bzw. 135,1 pro 100.000 PJ; Männer und Frauen ohne Diabetes: 41,0 bzw. 15,4 pro 100.000 PJ). Dagegen war das relative Risiko anders als bei der Studie aus Mettmann [Icks et al.] heterogen bei Männern und Frauen (Männer: 4,6 (95% KI: 3,6-5,8); Frauen: 8,8 (5,5-14,0).

Aufgrund des relativ kurzen Beobachtungszeitraums war es in beiden Studien nicht möglich, eine valide Aussage zur zeitlichen Entwicklung der RRT-Inzidenzrate und Erreichung der St. Vincent Ziele zu machen. Daneben war die Repräsentativität der Studienbevölkerung sehr eingeschränkt, da das Kollektiv aus nur einem einzigen Landkreis bzw. aus Versicherten einer einzelnen Krankenkasse bestand. Ferner war die Validität der Schätzung der Diabetesprävalenz bei der Studie aus Mettmann eingeschränkt, da sie auf Daten des früheren regionalen Diabetesregisters aus Ost-Berlin 1988 basierte.

International haben vor allem in den USA und Spanien viele Studien den zeitlichen Trend der RRT-Inzidenz in der Population mit und ohne Diabetes untersucht [Narres et al. 2016, Burrows et al. 2005, Burrows et al. 2010, Burrows et al. 2014, Burrows et al. 2017, CDC 2010 USA and Puerto Rico, CDC 1992, Jones et al. 2005, Muntner et al. 2003, Gregg et al. 2014, Comas et al. 2012, Lorenzo et al. 2010]. In beiden Ländern beobachtete man zunächst einen Anstieg der RRT-Inzidenz und später einen Rückgang, wobei der Rückgang in den USA bereits in den 1990ern erkennbar war; in Spanien hingegen erst in den 2000ern. Diese Studien zählten bei Menschen mit Diabetes allerdings nur die diabetische Nephropathie als Ursache für RRT, welche nur etwa die Hälfte aller RRT Ereignisse bei Menschen mit Typ 2 Diabetes ausmacht [Assogba et al. 2014, Burrows et al. 2017]. Somit war ein valider Vergleich mit der Bevölkerung ohne Diabetes in diesen Studien nicht möglich.

International gibt es bislang lediglich drei bevölkerungsbezogene Studien aus Kanada, Italien und Australien, welche ab den 90er Jahren die RRT-Inzidenz in der Bevölkerung mit und ohne Diabetes über einen längeren Zeitraum untersucht hatten mit Erfassung der RRT bei Menschen mit Diabetes unabhängig von der vorliegenden Ursache [Lok et al. 2004, Giorda et al. 2018, Koye et al. 2019]. Die Ergebnisse dieser drei Studien waren kontrovers. So fand die Studie aus Kanada zwischen 1994 und 2000 einen moderaten Rückgang der RRT-Inzidenzrate um 0,1 Prozent pro Jahr bei Personen mit Diabetes, während bei Menschen ohne Diabetes diese Zahl um etwa 0,5 Prozent pro Jahr anstieg. Das Risiko für Personen mit Diabetes war trotz des gegenläufigen Trends immer noch 12-fach erhöht im Vergleich zu Personen ohne Diabetes [Lok et al. 2004]. Die italienische Studie beobachtete dagegen keinen konsistenten Zeittrend zwischen 2004 und 2013 weder in der Bevölkerung mit Diabetes noch bei Menschen ohne Diabetes mit einer etwa 8-mal so hohen RRT-Inzidenz bei Menschen mit Diabetes verglichen zu Menschen ohne Diabetes [Giorda et al. 2018]. Die Studie aus Australien, welche bei den Zeittrends zusätzlich zwischen Typ1 und Typ2 Diabetes unterschied, fand eine etwa konstant bleibende RRT-Inzidenz zwischen 2002 und 2013 nur in der Bevölkerung ohne Diabetes und mit Typ 1 Diabetes [Koye et al. 2019]. Dagegen sah man dort einen deutlichen Anstieg bei Menschen mit Typ 2 Diabetes. Dabei war dieser Anstieg nur signifikant bei jüngeren (< 50 Jahre) und älteren (>= 80 Jahre).

Amputation

Eine Untersuchung der Inzidenzrate von allen Amputationen der unteren Extremität fand in Deutschland bereits in den 1990er Jahren statt. Neben der Inzidenz aller Amputationen interessierte meist auch die Untersuchung der Inzidenz von Major-Amputationen (Amputationen an der unteren Extremität, die in der Regel durch oder proximal des Sprunggelenks durchgeführt sind) sowie gelegentlich auch Minor-Amputationen (Amputationen unterhalb des Sprunggelenks). Die Inzidenzrate für alle sowie Major-Amputationen wurde im Zeitraum 1990-1991 bzw. 1994-2005 untersucht basierend auf den Daten der Leverkusen Amputationsreduktion Studie (LARS), welche nahezu alle erstmals aufgetretenen nicht traumatischen Amputationen der unteren Extremitäten in Leverkusen (ca.

160.000 Einwohner) erfasste [Trautner et al. 2007]. In dieser Studie wurde pro Person die erste jemals beobachtete Amputation gezählt. Die Inzidenzrate für eine jegliche Amputation sank um 2,4 Prozent pro Jahr (95% KI: 0,04%-4,2%) bei Personen mit Diabetes. Bei Major-Amputationen war dieser Rückgang noch deutlicher ausgeprägt: (3 Prozent pro Jahr; 0,03% - 5,7%). Im Gegensatz dazu konnte keine signifikante Veränderung der Inzidenzrate festgestellt werden bei Personen ohne Diabetes. Menschen mit Diabetes wiesen ein deutlich höheres Risiko im Vergleich zu Personen ohne Diabetes auf. Das korrespondierende relative Risiko sank signifikant um 5 Prozent im Beobachtungszeitraum (p-Wert Poisson-Modell mit Interaktion Diabetes*Zeit = 0,0078), wobei es aufgrund der kleinen Fallzahl erheblich zwischen 80 (in 1996) und 9 (in 2003 und 2004) schwankte. Ein ähnlicher Verlauf wurde auch bei Major-Amputationen beobachtet.

Neben der LARS Studie fand eine Untersuchung der Amputation-Inzidenzrate zwischen 1.1.2005 und 31.12.2007 mit Hilfe der Krankenkassendaten der GEK (ca. 1,6 Millionen Personen) statt [Icks et al 2009]. Die geschätzte Amputationsinzidenz lag bei Männer und Frauen mit Diabetes bei 176,5 (95% KI: 156.0-196.9) bzw. 76,9 (95% KI: 61.9-91.8) pro 100.000 PJ und bei Männer und Frauen ohne Diabetes bei 20,0 (95% KI: 17.0-23.1) bzw. 13,4 (95% KI: 10.7-16.2) pro 100.000 PJ. Das Personen mit und ohne Diabetes vergleichende relative Risiko, welches bei Männern und Frauen bei 8,8 (95% KI 7,3-10,7) bzw. 5,7 (4,3-7,6) lag, war somit etwas niedriger als in der Studie aus Leverkusen, bedeutet aber immer noch ein signifikant und klinisch relevant höheres Risiko für Menschen mit Diabetes. Auch in dieser Studie waren die Ergebnisse vergleichbar, wenn nur Major-Amputationen gezählt wurden.

Darüber hinaus untersuchte eine dritte Studie in Deutschland die Inzidenz aller Amputationen der unteren Extremitäten sowie Major und Minor-Amputationen zwischen 2007 und 2013 basierend auf Krankenkassendaten der AOK Rheinland/Hamburg [May et al. 2015]. Die Amputationsinzidenz sank von 504 pro 100.000 PJ auf 419 mit einem besonders deutlichen Rückgang bei Major-Amputationen von 217 auf 126 ($p< 0,0001$).

Die Repräsentativität aller drei Studien war eingeschränkt, da die Studienpopulation entweder aus einer Stadt oder aus Versicherten einer einzelnen Krankenkasse bestand. Bei der LARS-Studie war darüber hinaus die Schätzung der Bevölkerung mit Diabetes durch die Verwendung des Diabetesregisters aus Ost-Berlin 1988 weder repräsentativ für die Region noch für den Beobachtungszeitraum, und es wurde keine Veränderung der Diabetesprävalenz berücksichtigt. Dagegen war es bei der Studie mit den GEK-Daten nicht möglich, die zeitliche Entwicklung der Amputationsinzidenz zu untersuchen. Bei den beiden Studien mit Krankenkassendaten wurde nicht die jemals erste Amputation gezählt. Während in der Studie mit den GEK-Daten zumindest alle Personen im Jahr vor der Beobachtungsperiode (d.h. im Jahr 2004) ereignisfrei sein mussten, wurde bei den AOK-Daten jede beobachtete Amputation als „erste“ Amputation gezählt. Die Studie mit den Daten der AOK Rheinland/Hamburg wies als weitere Limitationen auf, dass es keinen Vergleich mit der der Bevölkerung ohne Diabetes gab und die Inzidenzraten nur roh, d h nicht nach Alter und Geschlecht adjustiert präsentiert wurden.

Im Gegensatz zu allen anderen mit Diabetes assoziierten Komplikationen gibt es weltweit bereits relativ viele bevölkerungsbezogene Studien, welche die Amputationsinzidenz innerhalb einer diabetischen und nicht-diabetischen Population analysiert haben [Narres et al. 2017]. Allerdings waren diese Studien sehr heterogen aufgrund der unterschiedlichen Art und Weise, wie eine Amputation gezählt wurde. Während einige Studie nur eine (die erste oder schwerste) Amputation pro Person zählten, berücksichtigen viele andere Studien jeden Krankenhausaufenthalt mit einer Amputation [Van Houtum et al. 1996, Lavery et al. 1996, Wrobel et al. 2001, Almaraz et al. 2012, Buckley et al. 2012, Gregg et al. 2014, Riandini et al. 2022]. Da es relativ häufig vorkommt, dass Personen in ihrem Leben mehrfach einen stationären Aufenthalt wegen einer Amputation haben, kann diese Zählweise zu einer Überschätzung der Amputationsinzidenz führen und erschwert die Vergleichbarkeit mit den Studien aus Deutschland [Van Houtum et al. 1997]. Andere Studien wiederum haben nur Major- bzw. Minor-Amputationen gezählt, so dass die Vergleichbarkeit zu anderen Studien auch hier eingeschränkt ist [Calle-Pascual et al. 2001, Canavan et al. 2008, Ikonen et al. 2010].

International gibt es sechs populationsbasierte Studien, welche die nach Alter adjustierte Inzidenz für alle Amputationen bei Personen mit und ohne Diabetes untersucht haben und dabei jedes Amputationsereignis pro Person gezählt haben [Gujral et al. 1993, Siitonen et al. 1993, Moris et al. 1998, Fosse et al. 2009, Lombardo et al. 2014, Déruaz-Luyet et al. 2020]. Die Studien aus Großbritannien und Finnland untersuchten die Amputationsinzidenz zwischen 1980 und 1985 bzw. 1978 und 1984 und fanden eine rund 10-fach höhere Inzidenzrate bei Menschen mit Diabetes im Vergleich zu Menschen ohne Diabetes [Gujral et al. 1993, Siitonen et al. 1993]. Die Studie aus Schottland untersuchte die Amputationsinzidenz in der Region Tayside in den Jahren 1993 und 1994 und fand eine etwa 12-mal so hohe Amputationsinzidenz in der Bevölkerung mit Diabetes [Morris et al. 1998]. In Frankreich fand eine nationenweite Studie aus dem Jahr 2003 das gleiche relative Risiko: die Amputationsinzidenz war ebenfalls etwa 12-mal so hoch in der Bevölkerung mit im Vergleich zu der ohne Diabetes [Fosse et al. 2009]. In einer Studie aus den USA war die Amputationsinzidenz zwischen 2010 und 2014 von Personen mit Typ 1 Diabetes 22,5-mal so hoch im Vergleich zu Menschen ohne Diabetes, während dieses relative Risiko bei Personen mit Typ 2 Diabetes nur 4,6-mal höher war [Déruaz-Luyet et al. 2020]. Für eine Beantwortung der in St. Vincent gestellten Frage, ob sich die Situation bei Menschen mit Diabetes verbessert hatte, eigneten sich diese Studien jedoch nicht aufgrund des zu kurzen Beobachtungszeitraums.

Die einzige Studie, welche die Gesamt-Amputationsinzidenz in der Population mit und ohne Diabetes mit dem Zählen einer Amputation pro Person über einen längeren Zeitraum untersucht hatte, war eine Studie aus Italien [Lombardo et al. 2014]. In Italien blieb die alters adjustierte Gesamt-Amputationsinzidenz zwischen 2001 und 2010 sowohl in der Bevölkerung mit als auch ohne Diabetes stabil mit einer etwa 10mal höheren Inzidenz bei Menschen mit Diabetes. Dagegen sank die Amputationsinzidenz mit 4 Prozent pro Jahr recht deutlich, wenn nur Major-Amputationen gezählt wurden.

Neben der Studie aus Italien gibt es vier weitere internationale Studien aus Finnland, Japan, Spanien und dem Vereinigten Königreich, welche die Inzidenz einer Major-Amputation pro

Person bei Menschen mit und ohne Diabetes zählten [Ikonen et al. 2010, Calle-Pascual et al. 2001, Kamitani et al. 2021, Canavan et al. 2008]. Der deutliche Rückgang der in Deutschland und Italien beobachteten Major-Amputationsinzidenz konnte in diesen Studien ebenfalls beobachtet werden [Ikonen et al. 2010, Calle-Pascual et al. 2001, Kamitani et al. 2021, Canavan et al. 2008]. In den drei Studien aus Europa war ein stärkerer Rückgang der Major-Inzidenzrate bei Menschen mit Diabetes als bei solchen ohne Diabetes zu verzeichnen. Dagegen sank diese Rate in Japan bei Menschen mit und ohne Diabetes in einem ähnlichen Ausmaß signifikant [Kamitani et al. 2021]. In allen Studien blieb die Major-Inzidenzrate signifikant erhöht bei Menschen mit Diabetes verglichen mit Menschen ohne Diabetes. In Japan und Italien war kein konsistenter Zeittrend des relativen Risikos zu erkennen mit einem mittleren Unterschied von 9,5 bzw. 6.4 [Lombardo et al. 2014, Kamitani et al. 2021]. In Finnland dagegen sank das relative Risiko bei Männern von 11,7 auf 7 und Frauen von 8,8 auf 4,5 [Ikonen et al. 2010]. Diese Studien waren jedoch beschränkt auf Major-Amputationen und ließen somit keine Aussage zum zeitlichen Trend von Gesamt-Amputationen zu. Darüber hinaus berichteten die Studien aus Spanien und dem Vereinigten Königreich keine altersadjustierten Inzidenzraten und relativen Risiken und waren somit nur bedingt vergleichbar mit den anderen Studien.

Bezüglich Minor-Amputation gibt es international nur drei Studien, die den zeitlichen Trend bei Menschen mit und ohne Diabetes analysiert und dabei eine Minor-Amputation pro Person gezählt haben [Lombardo et al. 2014, Calle-Pascual et al. 2001, Kamitani et al. 2021]. In Spanien sank die Inzidenzrate sowohl bei Menschen mit als auch ohne Diabetes [Calle-Pascual et al. 2001]. In Italien dagegen blieb sie unverändert bei Menschen mit Diabetes während sie sogar leicht angestiegen ist bei Menschen ohne Diabetes [Lombardo et al. 2014]. In Japan blieb sie ebenfalls unverändert sowohl bei Menschen mit als auch ohne Diabetes [Kamitani et al. 2021]. Das Menschen mit und ohne Diabetes vergleichende relative Risiko war in beiden Studien mit 14,9 in Japan bzw. 19,4 in Italien sehr hoch und blieb jeweils über den Studienzeitraum stabil. Die Studie aus Spanien berichtete auch hier keine altersadjustierten Inzidenzraten und relativen Risiken [Calle-Pascual et al. 2001].

Herzinfarkt

Bereits in den 1980er Jahren fand in Deutschland eine prospektive Studie statt, welche die kumulative Herzinfarktinzidenz bei Männern zwischen 35 und 64 Jahren in Münster getrennt nach Diabetesstatus schätzte [Buyken et al. 2007]. In dieser Studie hatten mit 13,3 Prozent Männer mit Diabetes mehr als doppelt so häufig einen Herzinfarkt als Männer ohne Diabetes (5,3 Prozent). In dieser Studie konnte allerdings kein zeitlicher Trend aufgrund der zu kurzen Beobachtungszeit geschätzt werden und es wurde keine Inzidenzrate untersucht. Ebenso war die Population zu selektiert, da nur Männer einer bestimmten Berufsgruppe eingeschlossen wurden.

Eine systematische Erfassung aller ersten Herzinfarkte inklusive Untersuchung des zeitlichen Trends bei Menschen von 25 bis 74 Jahren zwischen 1985 und 2006 fand in der Region Augsburg mit Hilfe des Augsburger Herzinfarktregisters statt [Icks et al. 2009]. Dabei sank zwischen 1985 und 2006 die Inzidenzrate bei Frauen mit Diabetes signifikant um 27 Prozent (95% KI 12%-39%) sowie bei Männer und Frauen ohne Diabetes um 34 Prozent (26% - 41%) bzw. 27 Prozent (13% - 38%)). Dagegen stieg die Inzidenzrate bei Männern mit Diabetes signifikant um 25 Prozent (7% - 45%). Dabei blieb die Inzidenzrate sowohl bei Männern (um Faktor 3) als auch bei Frauen mit Diabetes (um Faktor 6) während des gesamten Zeitraumes signifikant erhöht im Vergleich zu Personen ohne Diabetes.

In dieser Studie war die Schätzung der Diabetesprävalenz eine Limitation, die auf Basis der KORA-Survey (Kooperativen Gesundheitsforschung in der Region Augsburg) Befragungen erfolgte. Die Diabetesprävalenz wurde unterschätzt, da sie bei TeilnehmerInnen des Surveys niedriger lag als bei NichtteilnehmerInnen [Kowall et al. 2017].

International untersuchten viele bevölkerungsbezogene Studien die Herzinfarktinzidenzrate in der Bevölkerung mit und ohne Diabetes [Adeniyi et al. 2002, Ballotari et al. 2017, Barengo et al. 2008, Carson et al. 2014, Eliasson et al. 2003, Folsom et al. 1997, Fujishima et al. 1996, Haffner et al. 1998, Hyvarinen et al. 2009, Hu et al. 2002, Juutilainen et al. 2004, Kokubo et al. 2010, Laakso et al. 1995, Lee et al. 2004, Liu et al. 2017, Lundberg et al. 1997, Manson et al.

1991, Matuleviciene-Anangen et al. 2017, Moe et al. 2014, Niskanen et al. 1998, Pajunen et al. 2005, Rautio et al. 2005, Rewers et al. 1993, Saito et al. 2011, Schramm et al. 2008, Tancredi et al. 2020, Vimanalanda et al. 2014, Wannamethee et al. 2011]. Auch in diesen Studien war das Personen mit und ohne Diabetes vergleichende relative Risiko durchweg signifikant größer als eins. Allerdings lag der relative Unterschied bei den meisten Studien zwischen 1,5 und 3 und somit etwas niedriger als in der deutschen Studie.

Ähnlich wie beim Schlaganfall war auch hier bei den meisten Studien der Beobachtungszeitraum zu kurz oder das Studiendesign ungeeignet, um den zeitlichen Trend der Inzidenzraten zu evaluieren. Bei anderen Studien wiederum wurden nur neuerkrankte Menschen mit Diabetes berücksichtigt, was die Vergleichbarkeit mit anderen Studien erschwerte [Hu et al. 2002, Wright et al. 2019, Lindhardsen et al. 2011].

Allerdings haben im Gegensatz zu Schlaganfall deutlich mehr Studien bereits einen zeitlichen Trend der Inzidenzrate bei Personen mit und ohne Diabetes untersucht mit sehr heterogenen Ergebnissen [Niskanen et al. 2020, Laverty et al. 2017, Chu et al. 2019, Gregg et al. 2014, Nedkoff et al. 2014, Gregg et al. 2019, Barengo et al. 2008, Carson et al. 2014, Rautio et al. 2005]. So berichteten einige Studien einen signifikanten und stärkeren Rückgang bei Menschen mit Diabetes im Vergleich zu Menschen ohne Diabetes [Niskanen et al. 2020, Chu et al. 2019, Gregg et al. 2014, Nedkoff et al. 2014], während andere nur einen Rückgang bei Menschen ohne Diabetes fanden [Laverty et al. 2017]. Eine Studie aus Schottland, die den Zeitraum 2006-2015 abdeckte, berichtete dagegen einen signifikanten Rückgang der Herzinfarktinzidenz sowohl bei Menschen mit als auch bei Menschen ohne Diabetes in einem ähnlichen Ausmaß [Read et al. 2019]. Weiterhin zeigten einige Studien unterschiedliche Ergebnisse bei Männer und Frauen. Eine Studie aus Finnland, welche die Herzinfarktinzidenzrate in zwei Kohorten mit einem Follow-up von 10 Jahren verglich, fand einen abnehmenden Zeittrend bei Männern mit Diabetes sowie bei Männern und Frauen ohne Diabetes, aber keine Veränderung bei Frauen mit Diabetes [Barengo et al. 2008]. Ähnliche Ergebnisse sah man in einer Studie aus den USA [4] [Carson et al. 2014]. Im Gegensatz dazu

fand eine schwedische Studie keine konsistenten zeitlichen Trends bei Männern und Frauen mit Diabetes sowie bei Frauen ohne Diabetes zwischen 1989 und 2000, aber einen signifikanten Rückgang bei Männern ohne Diabetes [Rautio et al. 2005]. Das Menschen mit und ohne Diabetes vergleichende relative Risiko lag in diesen Studien zwischen 2 in Schottland [Read et al. 2019] und 6 in Finnland [Niskanen et al. 2020].

Eine große Limitation bei den meisten Studien war die nicht vollständige Erfassung aller Herzinfarktereignisse, da entweder nur hospitalisierte Herzinfarkte [Laverty et al. 2017, Chu et al. 2019, Gregg et al. 2014, Nedkoff et al. 2014, Gregg et al. 2019] oder nur fatale Ereignisse erfasst wurden [Niskanen et al. 2020]. Drei weitere Studien erfassten fatale und nicht-fatale Herzinfarkte, allerdings nur bei Menschen unter 65 Jahren [Barengo et al. 2008, Rautio et al. 2005, Carson et al. 2014].

2.2 Forschungsbedarf

Beim Stand der Forschung offenbarte sich, dass bisher durchgeführte Studien eine Reihe von methodischen Limitationen aufwiesen. So war es bislang nur sehr eingeschränkt möglich, valide Aussagen hinsichtlich der in St. Vincent formulierten Frage zu machen, ob die Inzidenzrate von mit Diabetes assoziierten Komplikationen in der Population mit Diabetes sich substantiell verringert hat. Die oft zu kurze Beobachtungszeit legte nahe, dass Studien mit einer deutlich längeren und konsistenten Erfassung der Inzidenzraten benötigt werden, um den zeitlichen Trend untersuchen zu können.

Bei bisher publizierten Studien wurde die Bevölkerung mit Diabetes häufig nicht valide geschätzt. Sehr viele internationale Studien waren nicht in der Lage, eine Inzidenzrate bezogen auf die Bevölkerung mit Diabetes zu schätzen, so dass folglich auch kein valider Vergleich zur Bevölkerung ohne Diabetes möglich war. Bei den in Deutschland durchgeführten Studien fand eine Schätzung der Diabetesprävalenz zwar meist statt. Allerdings war aufgrund der Verwendung des regionalen Diabetesregisters aus Ost-Berlin in 1988 bei Studien, die

Register- oder Sozialdaten nutzten, diese weder repräsentativ für die Studienpopulation noch aktuell. Da längere Beobachtungszeiträume benötigt werden, ist es darüber hinaus erforderlich, die Diabetesprävalenz nicht nur zu einem fixen Zeitpunkt, sondern für jedes Kalenderjahr des Beobachtungszeitraumes zu kennen oder zumindest valide abschätzen zu können. Dies erscheint geboten da allgemein anerkannt ist, dass die Diabetesprävalenz des bekannten Diabetes in Deutschland in den letzten Dekaden unabhängig von der Alterung der Bevölkerung zugenommen hat [Heidemann et al. 2013, Goffrier et al. 2017]. Aufgrund des Fehlens eines nationalen Diabetesregisters ist es erforderlich, über andere Datenquellen die Diabetesprävalenz bestmöglich zu schätzen. Dieses sollte bei Krankenkassendaten mit Hilfe eines geeigneten Algorithmus erfolgen. Im Falle der Nutzung von Primärdaten – wie z.B. Registern – ist es dagegen notwendig, die Diabetesprävalenz über externe Datenquellen zu eruieren. Dies können beispielsweise aktuellere Surveys sein, welche die Bevölkerung mit Diabetes in einer möglichst für die Studienpopulation repräsentativen Population im Beobachtungszeitraum schätzen. Um den Einfluss von Alter und Geschlecht auf die Diabetesprävalenz miterfassen zu können, sollten diese darüber hinaus für Männer und Frauen sowie verschiedene Altersklassen geschätzt werden.

Weiterhin war die Erfassung des ersten Ereignisses einer mit Diabetes assoziierten Komplikation sehr häufig in bisherigen nationalen wie internationalen Studien nicht vollständig oder vergleichbar mit anderen Studien. Dabei wurden insbesondere bei Schlaganfall und Amputation oft nur Subtypen der mit Diabetes assoziierten Komplikation (z. B. nur ischämischer Schlaganfall, nur Major-Amputation) erfasst. Bei Herzinfarkten konnten oft fatale Ereignisse nicht registriert werden. Hinzu kommt, dass bei der Erfassung häufig die hochbetagten Altersgruppen nicht befragt wurden. Studien zu RRT und Amputationen zählten dagegen häufig nur durch Diabetes ursächlich verursachte Komplikationen. Somit waren Studien erforderlich, welche mit Diabetes assoziierte Komplikationen vollständig über möglichst alle Altersgruppen zählten und unabhängig davon, ob Diabetes Erkrankungsursache war oder nicht. Bei Studien zum Herzinfarkt erscheint es darüber hinaus geboten, fatale Ereignisse systematisch miteinzuschließen. Eine weitere Limitation beim Zählen von mit

Diabetes assoziierten Komplikationen war das zuverlässige Erfassen der Erstereignisse pro Person insbesondere bei den Outcomes Amputation, Schlaganfall und Herzinfarkt, welche mehrfach pro Person auftreten können. So konnte in einer Studie beobachtet werden, dass bei nur 64 Prozent aller Personen mit Amputation die in diesem Jahr durchgeführte Amputation auch tatsächlich die erste war (van Houtum et al. 1997). Hier sind Registerdaten erforderlich, welche ermöglichen, die erste aufgetretene Komplikation pro Person systematisch zu erfassen. Falls Krankenkassendaten verwendet werden, besteht die Notwendigkeit, mit der begrenzten vorherigen Beobachtungszeit – man spricht von Linkszensierung – methodisch bestmöglich umzugehen. Das Problem dabei ist, dass die Linkszensierung die Schätzung des zeitlichen Trends verzerrt, da die Überschätzung der wahren Inzidenz zu Beginn am stärksten ist und im Laufe des Beobachtungszeitraumes abnimmt.

Viele v.a. internationale und Studien aus früheren Jahren schätzten nur rohe, d. h. nicht altersadjustierte Inzidenzraten. Dies führte insbesondere zu einer Überschätzung des relativen Risikos zwischen den Populationen mit und ohne Diabetes, da Menschen mit Typ 2 Diabetes meist älter sind und aufgrund ihres Alters häufiger erkranken als Personen ohne Diabetes. Daher sollten Studien nach Alter standardisierte Inzidenzraten schätzen, um den Alterseffekt adäquat aus der Inzidenzschätzung herauszurechnen und vergleichbarer mit anderen Studien zu sein.

Schließlich ist eine generelle Limitation vieler nationaler wie internationaler Studien die Repräsentativität der Studienpopulation, welche sich oft entweder auf eine kleinere Region, ein Kollektiv von Versicherten einer Krankenkasse oder eine bestimmte Altersgruppe beschränkte. Dies erfordert Studien mit einem möglichst nationenweiten repräsentativen Kollektiv, welches möglichst alle Altersgruppen umfasst.

3 Thema und Forschungsfragen der verwendeten Forschungsarbeiten

3.1 Wichtige Forschungsaspekte

In den der Habilitationsarbeit zu Grunde liegenden Forschungsarbeiten ging es darum, aktuelle und längere Zeiträume überdeckende Daten zu den Trends der Inzidenz diabetes-assoziierter Komplikationen in diabetischer und nicht diabetischer Population zu identifizieren und dabei neue Methoden zu erarbeiten, um die vorstehend erörterten Limitationen zu adressieren. Im Einzelnen waren diese methodischen Arbeiten:

1. Die Erschließung neuer und Erweiterung bestehender Datenquellen zur Abbildung der Endpunkte
2. Die verbesserte Operationalisierung der Endpunkte
3. Die Entwicklung von Methoden zum Umgang von datenspezifischen Merkmalen wie beispielsweise der Linkszensierung von Krankenkassen zur Schätzung valider Trends
4. Die Erarbeitung einer validen Schätzung der diabetischen Bezugspopulation

3.2 Zielsetzungen der Forschungsarbeiten

Die Hauptzielsetzung der vorliegenden Originalarbeiten ist die Untersuchung der zeitlichen Entwicklung der Inzidenzrate von mit Diabetes assoziierten Komplikationen bei Personen mit und ohne Diabetes sowie deren Vergleich. In den vorliegenden Originalarbeiten werden die Inzidenzen von Erblindung, Schlaganfall, RRT als Marker für terminale Niereninsuffizienz und Amputation analysiert. Um die St. Vincent Ziele vollständig abzubilden, wird zudem die Inzidenz von Herzinfarkten berichtet. Dabei ist das zentrale Ziel aller Arbeiten, Aussagen treffen zu können, ob die in St. Vincent geforderte Reduktion der Inzidenzraten – insbesondere in der Bevölkerung mit Diabetes – tatsächlich beobachtet werden konnte. Dabei interessierte

vorrangig, ob die Inzidenzraten im Vergleich mit der Bevölkerung ohne Diabetes (relatives Risiko) zurückgegangen sind. Ein besonderer Fokus liegt dabei auf dem Finden adäquater Datenquellen, welche die oben genannten methodischen Limitationen bestmöglich beseitigen können. Dazu bieten sich Datenquellen an, bei denen über einen längeren Zeitraum das Erstereignis o.g. Komplikationen bei Personen mit und ohne Diabetes vollzählig in einer möglichst repräsentativen Bevölkerung analysiert wird. Des Weiteren werden Datenquellen identifiziert, mit denen die Bezugspopulation mit und ohne Diabetes möglichst adäquat geschätzt werden kann. Darüber hinaus ist ein Ziel der Forschungsarbeiten, die o.g. Zielgrößen in verschiedenen Datenquellen verschiedener Länder bzw. Regionen möglichst einheitlich zu definieren, um Ergebnisse miteinander vergleichen zu können. Dabei wird insbesondere bei der Untersuchung der Amputationsinzidenz nach Lösungsansätzen gesucht, adäquat mit der Problematik der Linkszensierung umzugehen.

Nachfolgend wird die Methodik der zugrundeliegenden Originalarbeiten bezüglich verwendeter Datenquellen, Definition bzw. Operationalisierung und Zählweise der Outcomes, Definition der Bevölkerung mit Diabetes sowie statistische Methoden kurz vorgestellt. Dabei beschränkt sich die Beschreibung auf Neuerungen gegenüber vorherigen Forschungsarbeiten. Anschließend werden die einzelnen Originalarbeiten mit deren Kernergebnissen nacheinander kurz beschrieben. Die Vorstellung erfolgt in chronologischer Reihenfolge wobei eine sich im Einreichungsprozess befindende Arbeit zu dem Outcome Herzinfarkt am Ende vorgestellt wird. Abschließend folgt eine zusammenfassende Betrachtung der Ergebnisse entlang der oben genannten Forschungsfragen samt Diskussion und Fazit.

Tabelle 1: Übersicht über Methoden in den verwendeten Originalarbeiten

Referenz	Studienperiode, Studienpopulation	Alters range (Jahre)	Outcome	Datenquelle	Zählweise	Definition der Population mit Diabetes
Claessen et al. 2018	2008-2012 22 von 45 Landkreise in Baden-Württemberg N ca. 4.800.000	Alle	Erblindung	Blindengeld - empfängerdaten	Erstereignis pro Person	GEDA- Survey 2009, 2010, 2012
Icks, Claessen et al. 2017	1998-2014 Erlangen N ca. 105.000	≥18	Schlaganfall	Registerdaten	Erstereignis pro Person	GNHIES98 Survey, DEGS1 Survey
Claessen et al. 2020	2002-2016 Kreis Mettmann (ohne Monheim, Langenfeld) N ca. 310.000	≥30	RRT	Dialysezentrum	Erstereignis pro Person	GNHIES98, DEGS1
Narres, Claessen et al. 2020	2010-2016 Versicherte der AOK und BKK N ca. 25 Millionen	Alle	RRT	Krankenkassendaten	Erstereignis pro Person	Köster-Algorithmus* für jedes Kalenderjahr (mit ambulanten Diagnosen)
Claessen et al. 2018	2008-2012 Versicherte der AOK, BKK und Barmer N ca. 34 Millionen	Alle	Amputation (Major, Minor)	Krankenkassendaten	Erstereignis pro Person pro Jahr	Köster-Algorithmus* für jedes Kalenderjahr (mit ambulanten Diagnosen)
Claessen et al. 2018	2009-2013 Alle Versicherte in Belgien N ca. 11 Millionen (99% der Bevölkerung Belgiens)	Alle	Amputation (Major, Major oberhalb Knie, Major unterhalb Knie, Minor)	Krankenkassendaten	Erstereignis pro Person pro Jahr	Eigener Algorithmus für jedes Kalenderjahr (ohne ambulante Diagnosen)
Publikation im Einreichungs-prozess:						
Claessen et al.	1985-2016 Region Augsburg N ca. 600.000	45-74	Herzinfarkt (fataler, nicht-fataler)	Registerdaten	Erstereignis pro Person	KORA-Surveys (S1, S2, S3, S4, F3, F4, FF4) ZI-Daten

*In Deutschland etablierter Algorithmus zwecks Identifikation von Menschen mit Diabetes in Krankenkassendaten, welcher auf quartalsweise erhobenen Abrechnungsdaten basiert [Köster et al. 2006]

Eigen erstellte Tabelle

3.3 Methodik

Tabelle 1 liefert einen Überblick über die Charakteristik der sechs in die Habilitationsschrift eingehenden Originalarbeiten und einer sich im Einreichungsprozess befindenden Arbeit, die im Sinne der vollständigen Abbildung der St. Vincent-Ziele ebenfalls in dieser Habilitationsschrift vorgestellt wird.

Verwendete Datenquellen

Bezüglich Erblindung kamen wie in früheren Studien Daten-Träger der Sozialhilfe in Baden-Württemberg zur Anwendung. Hier bestand gegenüber der früheren Studie allerdings die Herausforderung, dass die Daten seit 2005 nicht mehr landesweit zusammengefasst vorlagen, sondern in allen 35 Landkreisen und 10 kreisfreien Städten erhoben werden mussten. Auch bezüglich Herzinfarkt und RRT kamen die gleichen Datenquellen zum Einsatz, wobei jeweils deutlich längere Zeiträume überblickt werden als in den Vorarbeiten. Bezüglich RRT konnten zusätzlich Krankenkassendaten gewonnen werden, in denen gepoolte Daten der im Vergleich zur GEK deutlich größeren AOK und BKK zur Anwendung kamen. Für die Untersuchung der Schlaganfallinzidenz konnte erstmals ein Schlaganfallregister als Datenquelle mit einer deutlich längeren Beobachtungsperiode gewonnen werden, so dass in Deutschland erstmals eine Untersuchung des zeitlichen Trends in der Bevölkerung mit und ohne Diabetes möglich war. Für die Untersuchung der Amputationsinzidenz kamen gleich zwei deutlich größere Datenquellen als die vorher genutzten GEK-Daten zur Anwendung. In beiden Arbeiten konnte erstmals die Untersuchung des zeitlichen Trends mit Krankenkassendaten realisiert werden. Während in der einen Forschungsarbeit die gepoolten Krankenkassendaten der AOK, BKK und Barmer die Datenquelle waren, verwendete die andere Originalarbeit nationenweite Sekundärdaten aus nahezu ganz Belgien.

Definition der Outcomes

Die Kriterien zwecks Identifikation von Erblindung, Schlaganfall, RRT, Amputation sowie Herzinfarkt waren nahezu identisch zu jenen früheren deutschen Studien aus den 1990er und 2000er Jahren [Icks et al. 1997, Trautner et al. 2001, Icks et al. 2011, Icks et al. 2011, Icks et

al. 2012, Icks et al. 2009, Icks et al. 2010, Hoffmann et al. 2011, Trautner et al. 2007]. Dabei konnten bezüglich Schlaganfall neben Schlaganfällen jeglicher Art anders als in der früheren Forschungsarbeit zusätzlich Auswertungen zum am häufigsten vorkommenden Schlaganfalltyp, dem ischämischen Schlaganfall (ICD-10: I63) erfolgen. Bei der Identifikation einer RRT mit gepoolten Krankenkassendaten konnte erstmals die neu eingeführte Diagnose N 18.5, welche bei den meisten Personen mit RRT gestellt wurde, berücksichtigt werden.

Zählweise der mit Diabetes assoziierten Komplikationen

In den in dieser Schrift vorgestellten Forschungsarbeiten war das Ziel, immer das Erstereignis pro Person zu erfassen, da die Zahl neu erkrankter Personen von besonderem Interesse war. *So* konnte bei den Forschungsarbeiten zu Schlaganfall, RRT sowie Herzinfarkt via Register- bzw. Dialysezentrumsdaten unmittelbar das Ereignis pro Person gezählt werden, da sich alle erkrankten Personen jeweils einer Befragung bzw. klinischen Untersuchung hinsichtlich möglicher vorheriger mit Diabetes assoziierter Komplikationen unterzogen. Ebenso war es möglich bei Erblindung ad hoc von einem Erstereignis pro Person zu sprechen, da eine Erblindung per Definition eine dauerhafte Störung des Sehvermögens ist und somit nur einmal im Leben auftritt. Bei der Auswertung der RRT über die Krankenkassendaten ist es zwar möglich, dass eine vorherige RRT pro Person sich ereignet. Allerdings kann dies nur im Falle einer terminalen Niereninsuffizienz nach einer Nierentransplantation vorkommen, was im Verhältnis zu allen RRT-Fällen sehr selten vorkommt.

Dagegen ist bei der Erfassung von Amputationen anhand von Krankenkassendaten die Zählweise ein wichtiges Kriterium. Amputationen treten häufig wiederholt auf (z.B. erst Amputation des rechten Fußes, später des ganzen rechten Beins, dann Amputation des linken Fußes). Vorherige Ereignisse sind jedoch in Krankenkassendaten wegen der Linkszensierung nur bedingt oder im Fall von Krankenversicherungswechsel gar nicht zu identifizieren. Eine Befragung von Versicherten ist theoretisch möglich, in der Praxis aber kaum durchführbar. Mit den deutschen Krankenkassendaten der hier vorgestellten Forschungsarbeit zur Amputationsinzidenz in Deutschland fand erstmals eine Überprüfung statt, ob die Annahme der einjährigen ereignisfreien Periode („Wash-Out“) aus den früheren Auswertungen mit den

GEK-Daten [Icks et al. 2011] zulässig ist. So konnte in den gepoolten Krankenkassendaten der AOK, BARMER GEK und BKK bei jenen Personen mit Amputation im letzten Jahr der Beobachtungsperiode (2012) untersucht werden, wie häufig frühere Amputationen in den fünf Jahren zuvor (2007-2011) aufgetreten waren. Dabei ergab sich, dass etwa 20 Prozent aller Personen mit Amputation bereits zuvor sich einer Amputation unterzogen hatten, die mehr als ein Jahr zurücklag. Darüber hinaus konnte festgestellt werden, dass dieser Anteil deutlich unterschiedlich ausfällt bei Personen mit und ohne Diabetes (24% vs. 15%), so dass ein Vergleich zwischen diesen beiden Personengruppen deutlich verzerrt wäre. Hinzu kommt, dass die Überschätzung der Inzidenzrate zu Beginn des Beobachtungszeitraums sich unterschiedlich stark im weiteren zeitlichen Verlauf auswirkt. So wäre eine Person mit vermeintlich erster Amputation im ersten Beobachtungsjahr 2008 nur mindestens ein Jahr ereignisfrei gewesen, während es bei einer Person im Jahr 2012 in der Regel, sofern sie durchgehend versichert war, bereits fünf Jahre waren. Infolgedessen würde die Inzidenzrate der ersten Amputation zu Beginn des Beobachtungszeitraumes deutlich stärker überschätzt werden als am Ende, so dass ein vermeintlich deutlicher Rückgang der Inzidenz nur vorgetäuscht würde.

In den hier vorgestellten Forschungsarbeiten war man dennoch bestrebt nur eine Amputation pro Person zu zählen, weil eine Amputation ein starker Prädiktor für alle folgenden Amputationsereignisse ist, so dass das Einbeziehen von Re-Amputationen zu verzerrten Ergebnissen führen kann. Anstatt nur die erste jemals aufgetretene Amputation pro Person zu zählen, erfolgte die Schätzung einer Inzidenzrate, indem im Zähler der Inzidenzrate für jedes Kalenderjahr die erste stattgefundene Amputation aufgeführt wurde. Dabei war es irrelevant, ob für die betreffende Person bereits Amputationen aus Vorjahren vorlagen. Ebenso blieben bei dieser Zählweise weitere im selben Kalenderjahr durchgeführte Re-Amputationen unberücksichtigt. Dies war von Bedeutung, da insbesondere während eines Krankenhausaufenthaltes mehrere Amputationen erfolgen können und sodann einzeln kodiert werden, was insbesondere bei der Amputation von Zehen häufig der Fall ist. Eine Berücksichtigung solcher Re-Amputationen würde ansonsten zu einer massiven

Überschätzung um mehr als den Faktor drei der hier interessierenden Inzidenzrate von einer Amputation pro Person führen [van Houtum et al. 1997]. Und selbst wenn nur jeder stationäre Aufenthalt mit einer Amputation gezählt wird, was viele Studien gemacht haben, ist die Überschätzung um etwa den Faktor zwei immer noch beträchtlich [van Houtum et al. 1997]. Im Nenner der Inzidenzrate wurden alle Personenzeiten von Patienten aufgeführt, die bei einer der betreffenden Krankenkassen im relevanten Zeitraum versichert waren. Dabei blieben auch Personen unter Risiko, welche sich bereits in einem früheren Jahr einer Amputation unterzogen hatten. Bei dieser Methodik – Inzidenzrate einer Amputation pro Jahr – konnte somit im Gegensatz zum früheren Ansatz – Inzidenzrate einer jemals ersten Amputation – eine Person mehrere Male in verschiedenen Kalenderjahren gezählt werden, wenn Amputationen in unterschiedlichen Jahren identifiziert wurden (z.B. Major-Amputation des rechten Beins in 2010, Major-Amputation des linken Beins in 2011). Bezüglich des Outcomes Major-Amputation wurde eine Person auch dann gezählt, wenn im selben Jahr bereits eine Minor-Amputation erfolgt war und umgekehrt. Der Vorteil der hier dargelegten Methodik besteht darin, dass jedes Jahr das gleiche Verfahren angewendet wird. Dadurch kommt es nicht zu einer Verzerrung bei der Analyse von zeitlichen Trends. Aufgrund der oben beschriebenen Problematik der Linkszensierung wurde entschieden, auch bei der Auswertung der Amputationsinzidenz in Belgien die Inzidenzrate für eine Amputation pro Jahr zu schätzen.

Definition Diabetes

In Deutschland gibt es kein Diabetesregister, so dass die Bevölkerung mit Diabetes durch externe Datenquellen geschätzt werden muss. Allerdings sind seit Ende der 1990er Jahre mehrere repräsentative bevölkerungsbezogene bundesdeutsche Surveys durchgeführt worden, mit welchen sich die Diabetesprävalenz in Deutschland für alle Altersklassen relativ gut schätzen lässt [RKI 2000, RKI 2013, RKI 2014, RKI 2015]. Bei allen Forschungsarbeiten, welche Sozialamt-, Register- und Dialysepraxisdaten benutzten, konnte daher nun erstmals die Diabetesprävalenz mit Hilfe repräsentativer bundesdeutscher Surveys geschätzt werden. Der Vorteil dieser Methode lag darin, dass die Diabetesprävalenz über mehrere Zeitpunkte geschätzt werden konnte, welche den Beobachtungszeitraum gut abgedeckt haben. Es war

somit erstmals in Deutschland möglich, zeitliche Änderungen der Diabetesprävalenz bei der Inzidenzschätzung von mit Diabetes assoziierten Komplikationen zu berücksichtigen.

Günstig war zudem, dass die Surveys BGS98 (1997-1999) und DEGS (2008-2011) jeweils die Beobachtungszeiträume der Zeittrends zu Schlaganfall (1998-2014) und RRT (2002-2016) relativ gut abgedeckt haben. Bei der Verwendung der BGS98- und DEGS-Daten bestand jedoch das Problem, dass Schätzungen der Diabetesprävalenz nur für Personen bis 80 Jahre verfügbar waren. Da jedoch insbesondere Schlaganfälle bei Personen über 80 Jahre besonders häufig auftreten, war es erforderlich, die Diabetesprävalenz auch für diese Altersklasse zu schätzen. Untersuchungen zweier Krankenkassen konnten zeigen, dass die Diabetesprävalenz mit zunehmendem Alter ab 80 Jahren in etwa gleichbleibt [Heidemann et al. 2013]. In Folge dessen wurde die Annahme getroffen, dass die Diabetesprävalenz für Personen über 80 Jahren der Diabetesprävalenz von Personen zwischen 70-79 Jahren entspricht. Für die Jahre zwischen den Surveys (2000-2007) wurde die Diabetesprävalenz linear interpoliert während für die Jahre nach dem letzten Survey (d. h. ab dem Jahr 2012) linear extrapoliert wurde.

Bei der Forschungsarbeit zum Thema Erblindungsinzidenz kamen für die Diabetesprävalenzschätzung die GEDA-Surveys aus den Jahren 2009, 2010 und 2012 zum Einsatz, welche den Beobachtungszeitraum 2008-2012 gut abdeckten. In der sich derzeit im Einreichungsprozess befindenden Forschungsarbeit zum Thema Herzinfarktinzidenz kommen dagegen die KORA Surveys S1, S2, S3, S4, F3, F4 und FF4 zum Einsatz. Dies weist den Vorteil auf, dass die Diabetesprävalenz unmittelbar aus derselben Studienregion geschätzt werden kann. Da allerdings die vorgenannten Surveys den Beobachtungszeitraum 1985-2016 nicht vollständig abdecken, werden für die Schätzung der Diabetesprävalenz der späteren Zeitperiode 2009-2016 Daten des Zentralinstituts für die kassenärztliche Versorgung (ZI) verwendet [Goffrier et al. 2017]. Vorteilhaft ist dabei, dass diese Daten über 80 Prozent der Bevölkerung der Region Augsburg erfassen und damit deutlich repräsentativer sind als die KORA-Surveys, die weniger als 5 Prozent der Bevölkerung berücksichtigen [Löwel et al. 2005]. Darüber hinaus ist inzwischen bekannt, dass die Diabetesprävalenz mit den KORA-Surveys

systematisch unterschätzt wurde [Kowall et al. 2017]. Um diese Unterschätzung auszugleichen, wird die Diabetesprävalenz des letzten KORA-Surveys FF4 aus den Jahren 2013 und 2014 mit jener Prävalenz der ZI-Daten aus denselben Jahren verglichen, und es werden Korrekturfaktoren berechnet, die mit den KORA-Prävalenzen multipliziert werden.

In den beiden Forschungsarbeiten zu Amputation sowie einer Forschungsarbeit zu RRT basierten die Auswertungen auf gesetzlichen Krankenkassendaten. Hier bestand der große Vorteil darin, dass für die Identifikation des Diabetesstatus bei den Personen mit Amputation bzw. RRT und in der Bevölkerung unter Risiko ein identischer Algorithmus zur Anwendung kam. Entsprechend fand die Identifikation von Diabetes in den deutschen Daten mit dem bereits etablierten Algorithmus von Köster statt, welcher auf quartalsweise erhobenen Abrechnungsdaten basiert [Köster et al. 2006]. Dieser bereits in früheren, auf GEK-Daten basierenden Studien angewandte Algorithmus konnte in den vorgestellten Forschungsarbeiten verbessert werden. So wurden die Kriterien zwecks Identifikation des Diabetes nicht nur zu einem fixen Zeitpunkt zu Beginn, sondern fortlaufend über den gesamten Beobachtungszeitraum abgefragt, um Menschen mit einem inzidenten Diabetes mit zu erfassen.

Statistische Methodik

Alle Auswertungen wurden sowohl für die gesamte Studienpopulation als auch getrennt für Männer und Frauen gerechnet, da mehrere Studien bereits für beide Geschlechter unterschiedliche Ergebnisse eruiert hatten [Rautio et al. 2005, Barengo et al. 2008]. Die Durchführung aller Auswertungen erfolgte eigenhändig mit der Statistiksoftware SAS Version 9.4 (TS1M5).

Die Schätzung der Inzidenzraten der mit Diabetes assoziierten Komplikationen erfolgten separat für jedes Jahr des Beobachtungszeitraumes in der Bevölkerung mit und ohne Diabetes, sowie in der Gesamtpopulation. Alle Inzidenzraten wurden nach Alter und Geschlecht adjustiert bzw. altersadjustiert für Männer und Frauen mit Hilfe der Methode der direkten Standardisierung. Für den Vergleich der Inzidenzraten zwischen Personen mit und ohne Diabetes wurden Inzidenzraten Ratios (IRR) berechnet.

Um Aussagen zur zeitlichen Entwicklung der Inzidenzrate von mit Diabetes assoziierten Komplikationen bei Personen mit und ohne Diabetes machen zu können, wurden getrennt für die Bevölkerungen mit und ohne Diabetes Poisson-Regressionsmodelle gerechnet. Die Untersuchung des zeitlichen Trends der RRT-Inzidenz mit den GKV-Daten erfolgte darüber hinaus separat für verschiedene Altersklassen. Dies war möglich aufgrund der sehr großen Studienpopulation. Hintergrund war, dass frühere Publikationen unterschiedliche Zeittrends der RRT-Inzidenz für verschiedene Altersklassen beobachteten [Gregg et al. 2014, Koye et al. 2019]. Aufgrund der sehr hohen Schwankungen der Herzinfarktinzidenz zwischen den einzelnen Jahren in den KORA-Daten, wird der Beobachtungszeitraum – anders als in früheren und den hier bereits publizierten Originalarbeiten – in 4-Jahres Intervalle (1985-1988, 1989-1992, 1993-1996, 1997-2000, 2001-2004, 2005-2008, 2009-2012. 2013-2016) unterteilt. Um der Forschungsfrage nachzugehen, ob eine mögliche Reduktion der Inzidenzrate der mit Diabetes assoziierten Komplikationen in der Bevölkerung mit Diabetes ausgeprägter war als in der Bevölkerung ohne Diabetes, erfolgte darüber hinaus die Durchführung weiterer Poisson-Modelle mit dem Interaktionsterm „Diabetesstatus*Zeit“. In den zugrundeliegenden Originalarbeiten wurde hierfür die Änderung des relativen Risikos pro Kalenderjahr geschätzt. Für alle Schätzer wurden zwecks Schätzung der Genauigkeit 95%-Konfidenzintervalle angegeben.

Weiterhin wurden mehrere Sensitivitätsanalysen durchgeführt, um mögliche Fehlerquellen abschätzen zu können, die aufgrund unvollständiger Datenerhebung oder des Studiendesigns nahelagen. So konnte bei den Auswertungen der Inzidenz des Schlaganfalls und der RRT die Diabetesprävalenz nur für den Zeitraum 1998 bis 2011 durch lineare Interpolation der Prävalenzschätzer aus den BGS98 und DEGS Studien bestimmt werden. Da in beiden Auswertungen der Beobachtungszeitraum darüber hinaus ging, ließ sich nicht ausschließen, dass die Extrapolation zu verzerrten Ergebnissen führt. Diese potentielle Fehlerquelle wurde kontrolliert, indem alle Analysen wiederholt wurden mit der Annahme, dass sich die Diabetesprävalenz ab 2011 als konstant darstellte. Bei der Untersuchung der Herzinfarktinzidenz wurde die Diabetesprävalenz der KORA-Surveys als zutreffend

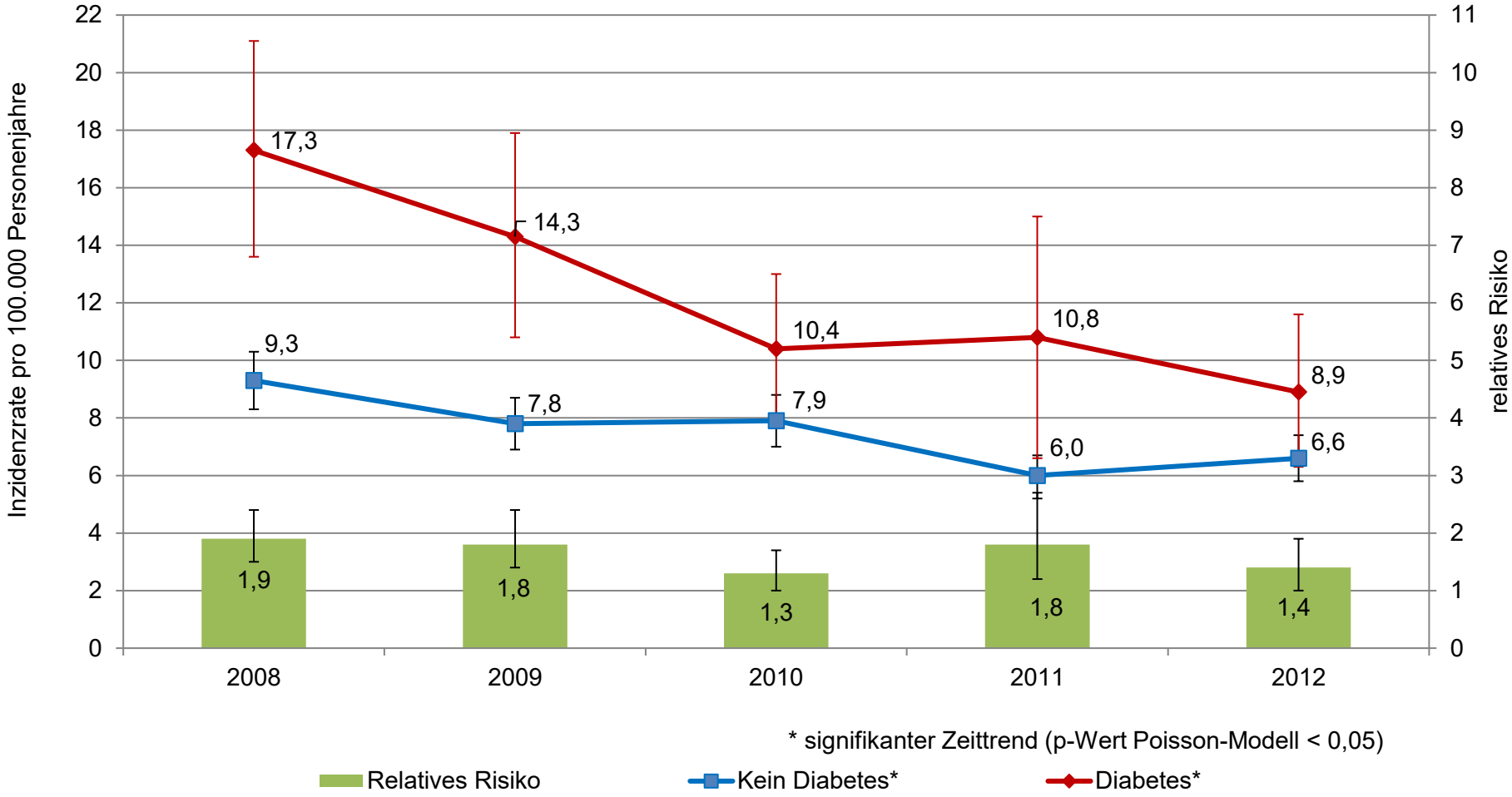
angenommen und für den gesamten Beobachtungszeitraum geschätzt, um herauszufinden, ob die Verwendung von zwei verschiedenen Datenquellen (KORA-Surveys, ZI-Daten) Auswirkungen auf den zeitlichen Trend hat.

Weiterhin konnte bei der Auswertung der Schlaganfallinzidenz mit dem Erlanger Schlaganfallregister bei etwa 10% aller Personen mit erstem Schlaganfall der Diabetesstatus nicht ermittelt werden. Aus diesem Grund wurden weitere Sensitivitätsanalysen gerechnet, wobei zum einen alle Personen mit unbekanntem Diabetes als Diabetiker und zum anderen als Menschen ohne Diabetes gezählt wurden.

4 Eigene Originalarbeiten

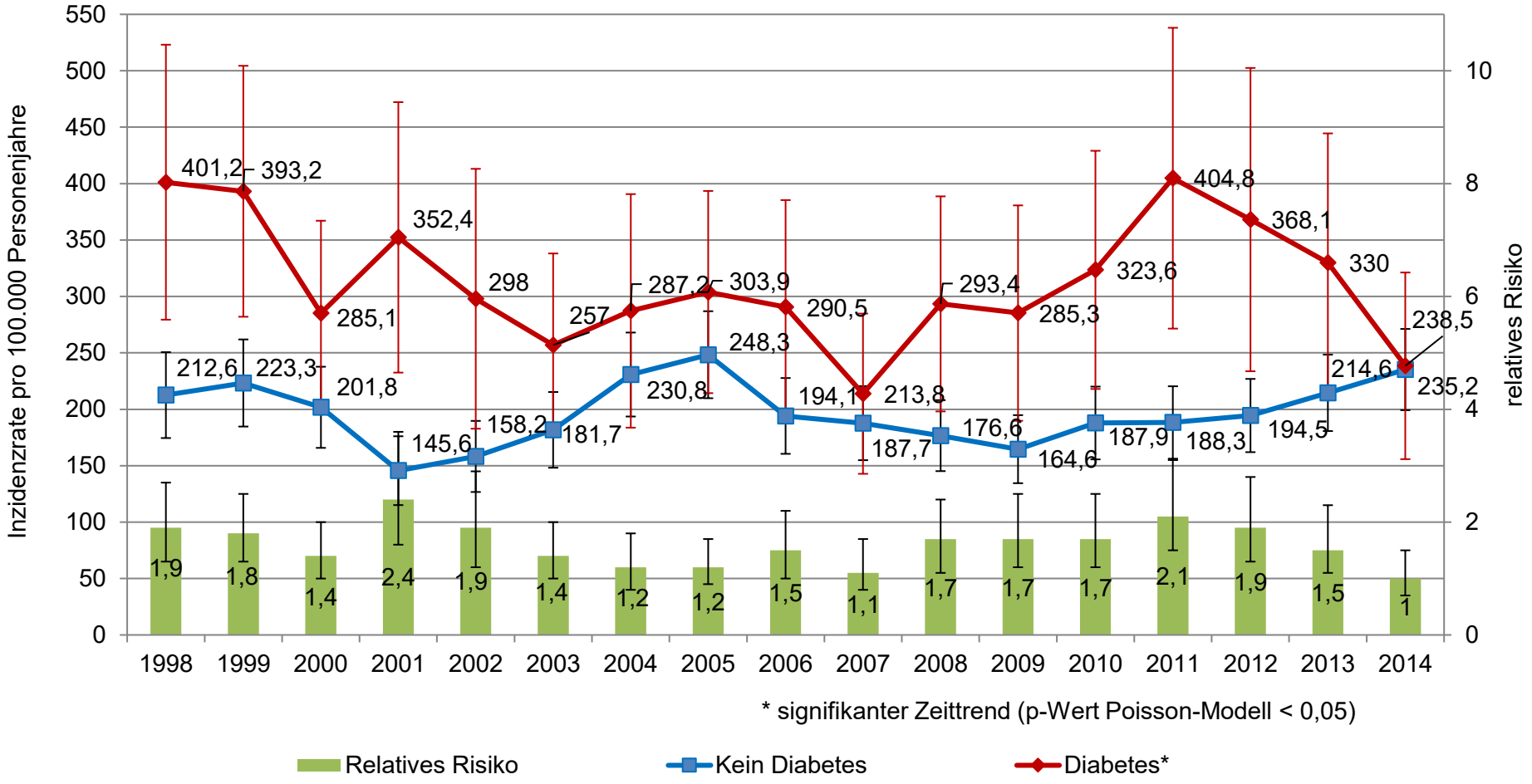
Die wichtigsten Ergebnisse aller verwendeten Originalarbeiten (Inzidenzraten, relative Risiken und zeitlicher Trend) sind nachfolgend in den Abbildungen 2 bis 11 dargestellt. Weiterhin werden hier zwecks vollständiger Abbildung der St. Vincent Ziele die wichtigsten Ergebnisse der sich im Einreichungsprozess befindenden Arbeit zum Outcome Herzinfarkt in den Abbildungen 12 bis 17 vorgestellt.

Abbildung 2: Inzidenzrate und relatives Risiko Erblindung Baden-Württemberg 2008-2012



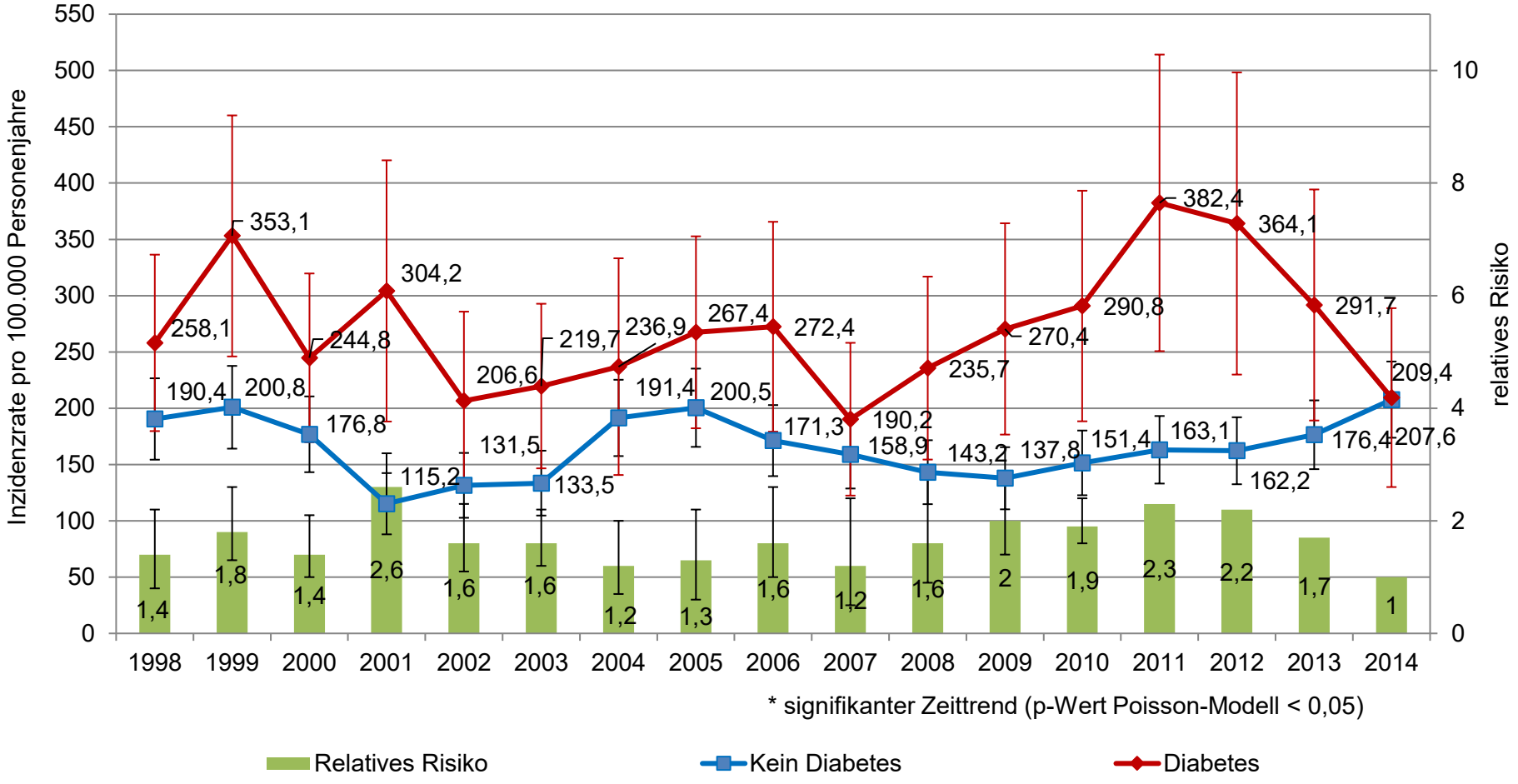
Eigen erstellte Abbildung

Abbildung 3: Inzidenzrate und relatives Risiko Schlaganfall (alle Typen) Erlangen 1998-2014



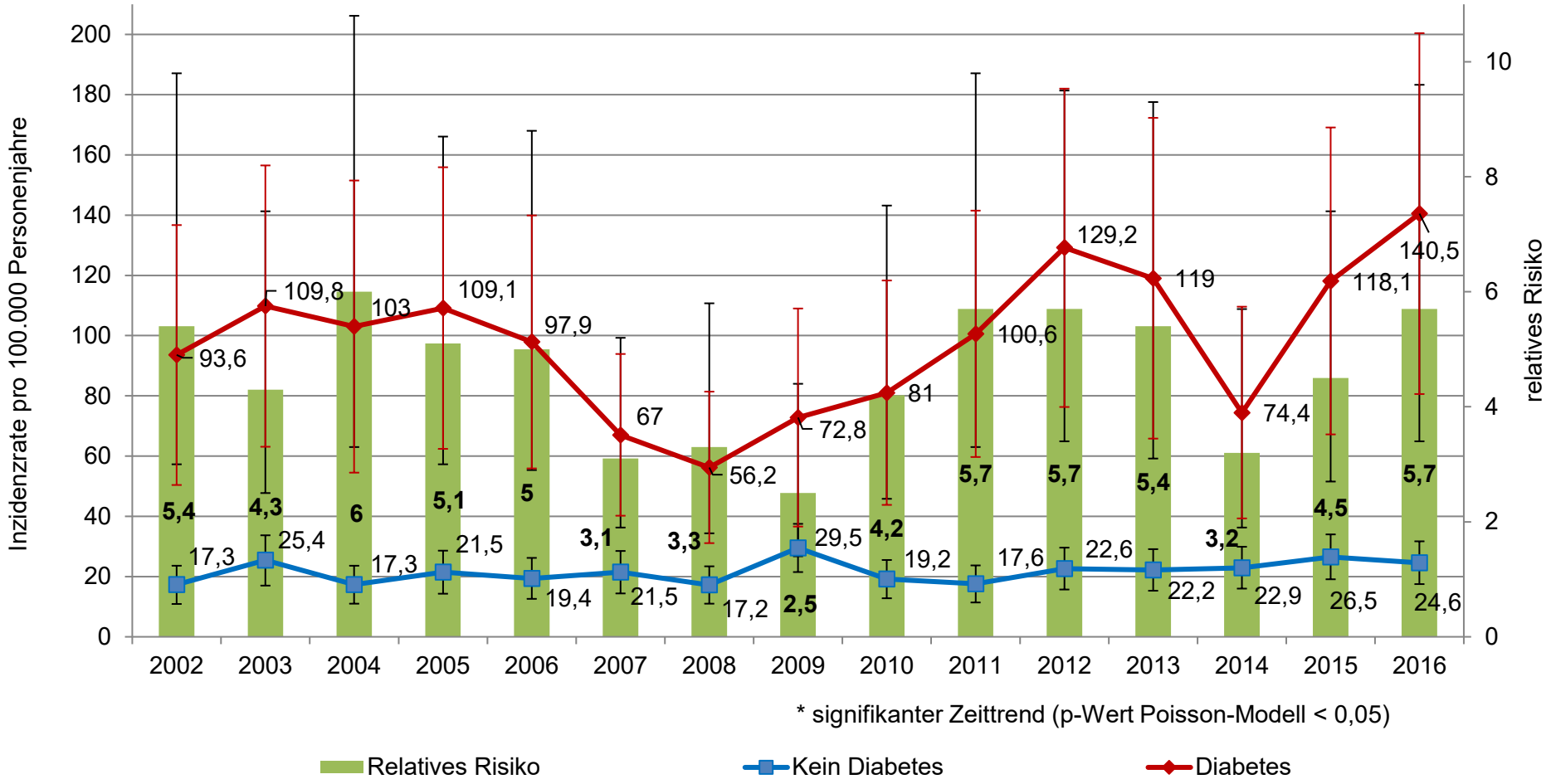
Eigen erstellte Abbildung

Abbildung 4: Inzidenzrate und relatives Risiko Ischämischer Schlaganfall Erlangen 1998-2014



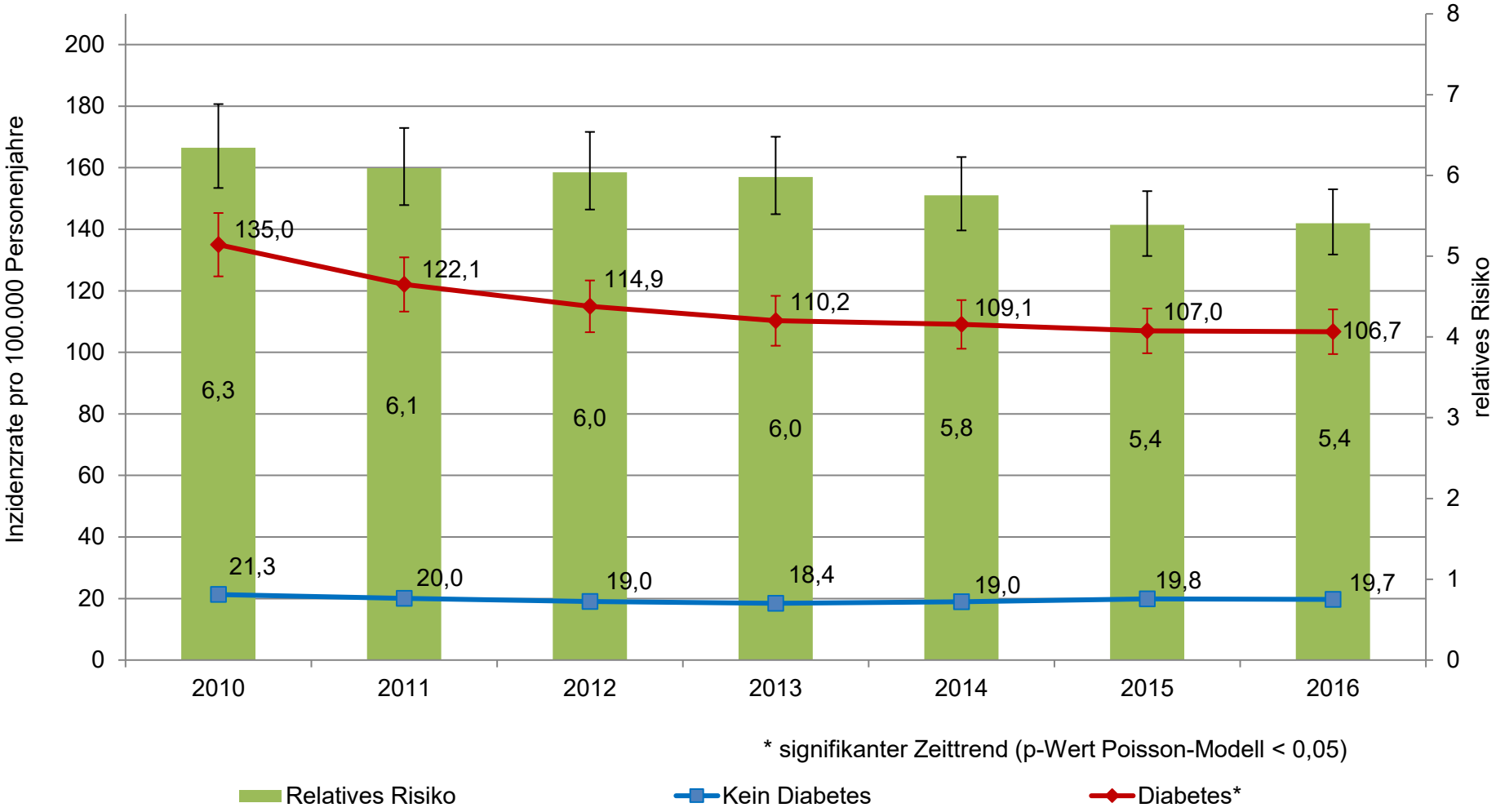
Eigen erstellte Abbildung

Abbildung 5: Inzidenzrate und relatives Risiko RRT Mettmann 2002-2016



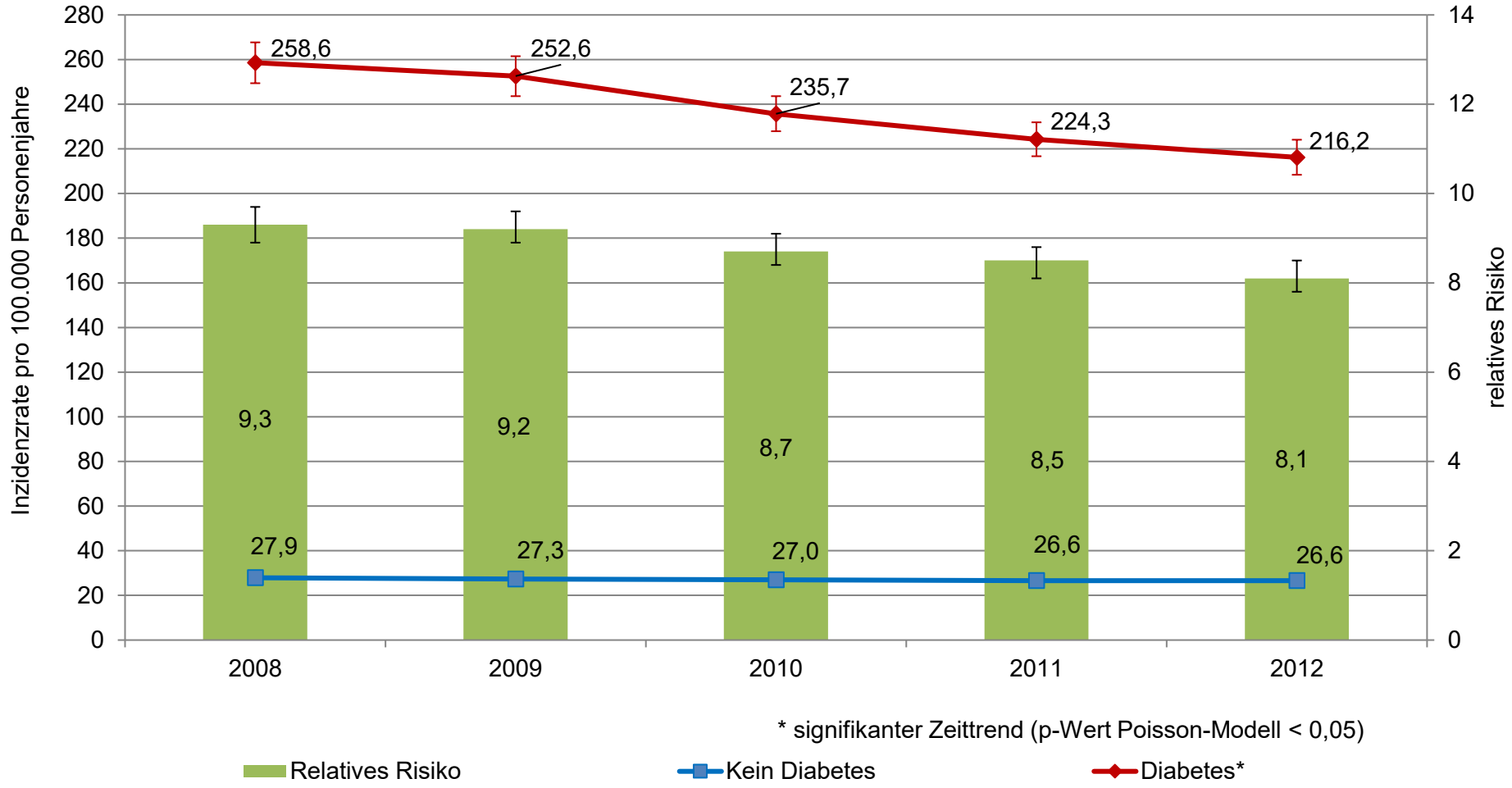
Eigen erstellte Abbildung

Abbildung 6: Inzidenzrate und relatives Risiko RRT GKV-Daten 2010-2016



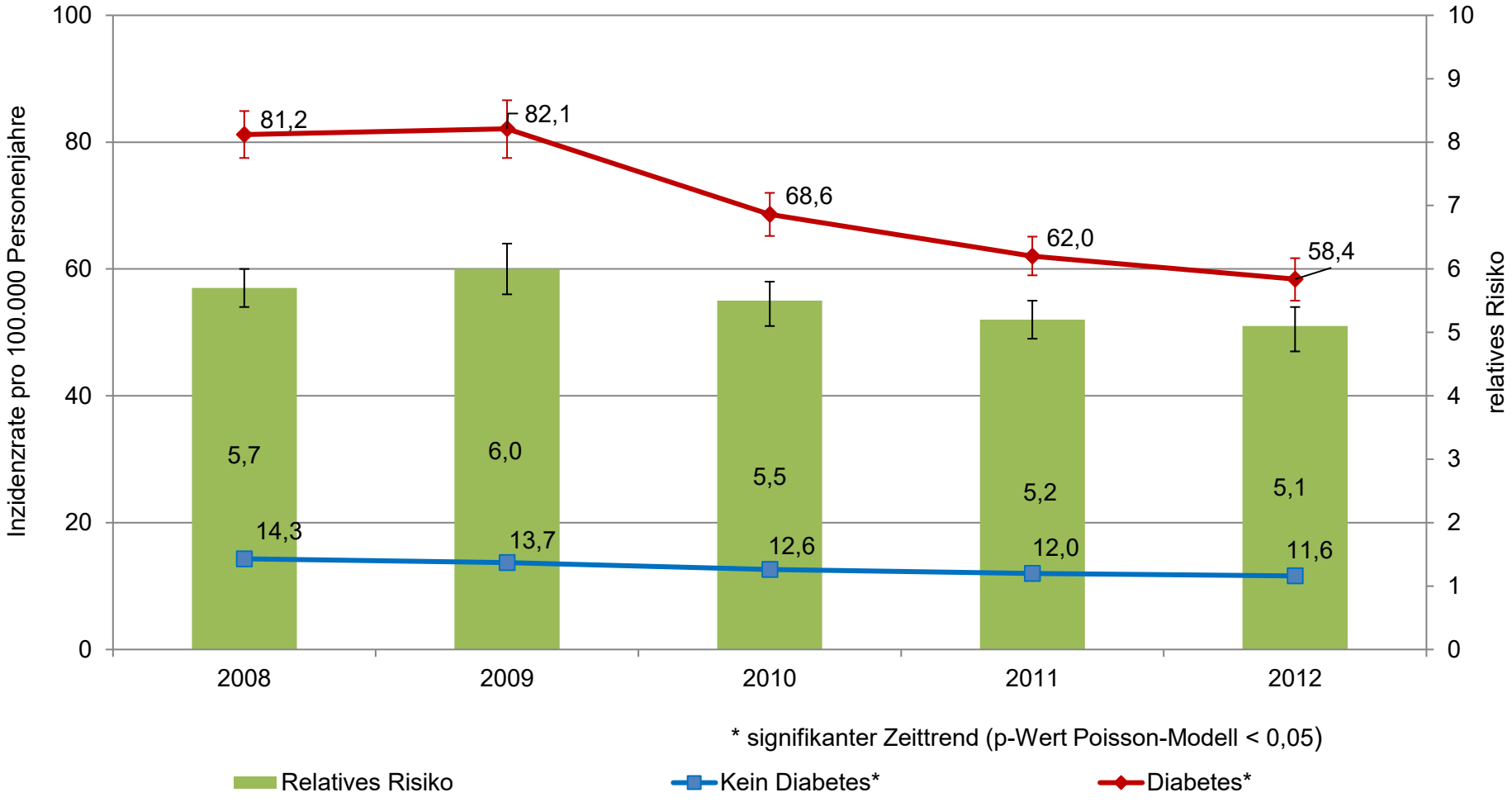
Eigen erstellte Abbildung

Abbildung 7: Inzidenzrate und relatives Risiko Amputationen (Major und Minor) GKV-Daten 2008-2012



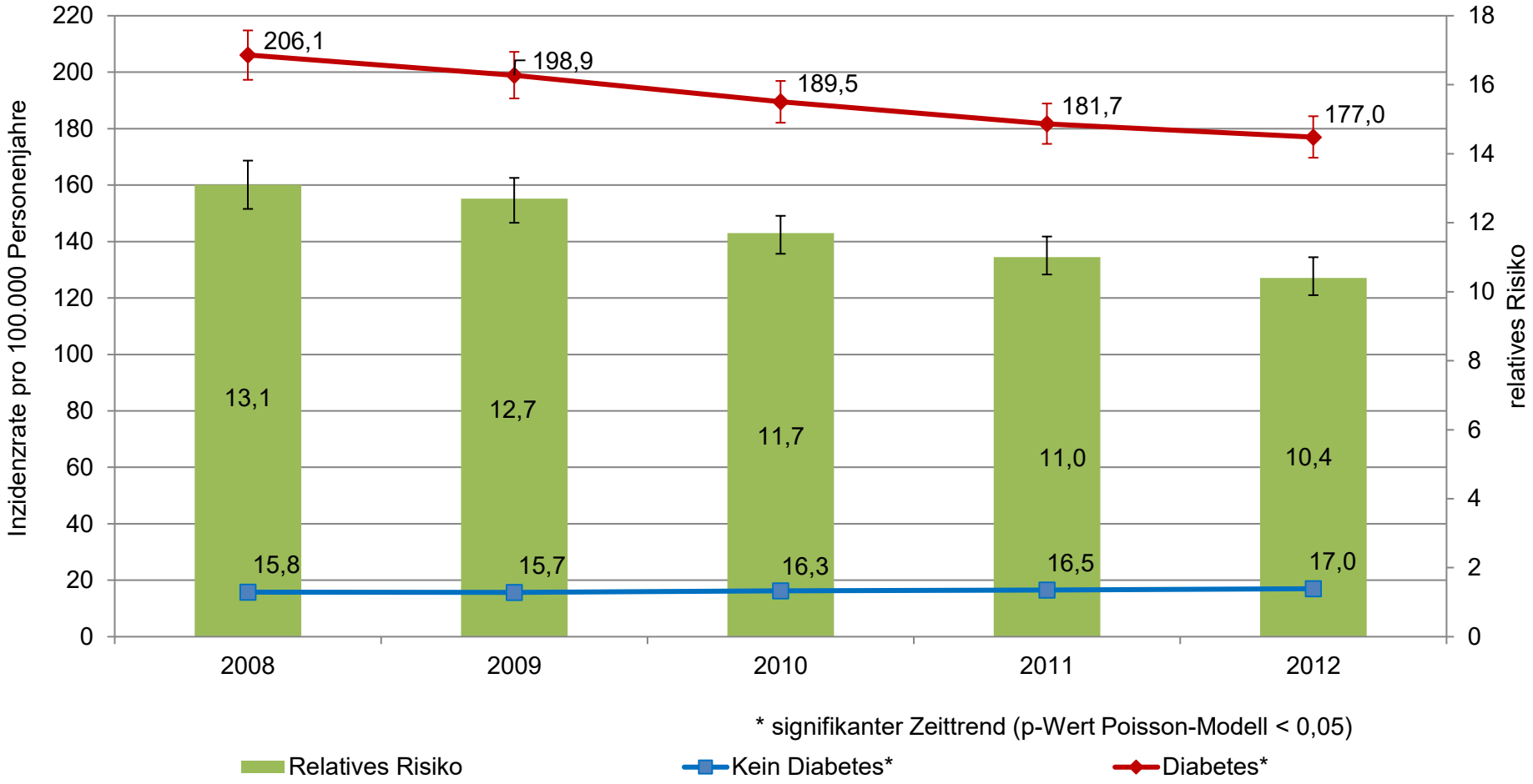
Eigen erstellte Abbildung

Abbildung 8: Inzidenzrate und relatives Risiko Major-Amputation GKV-Daten 2008-2012



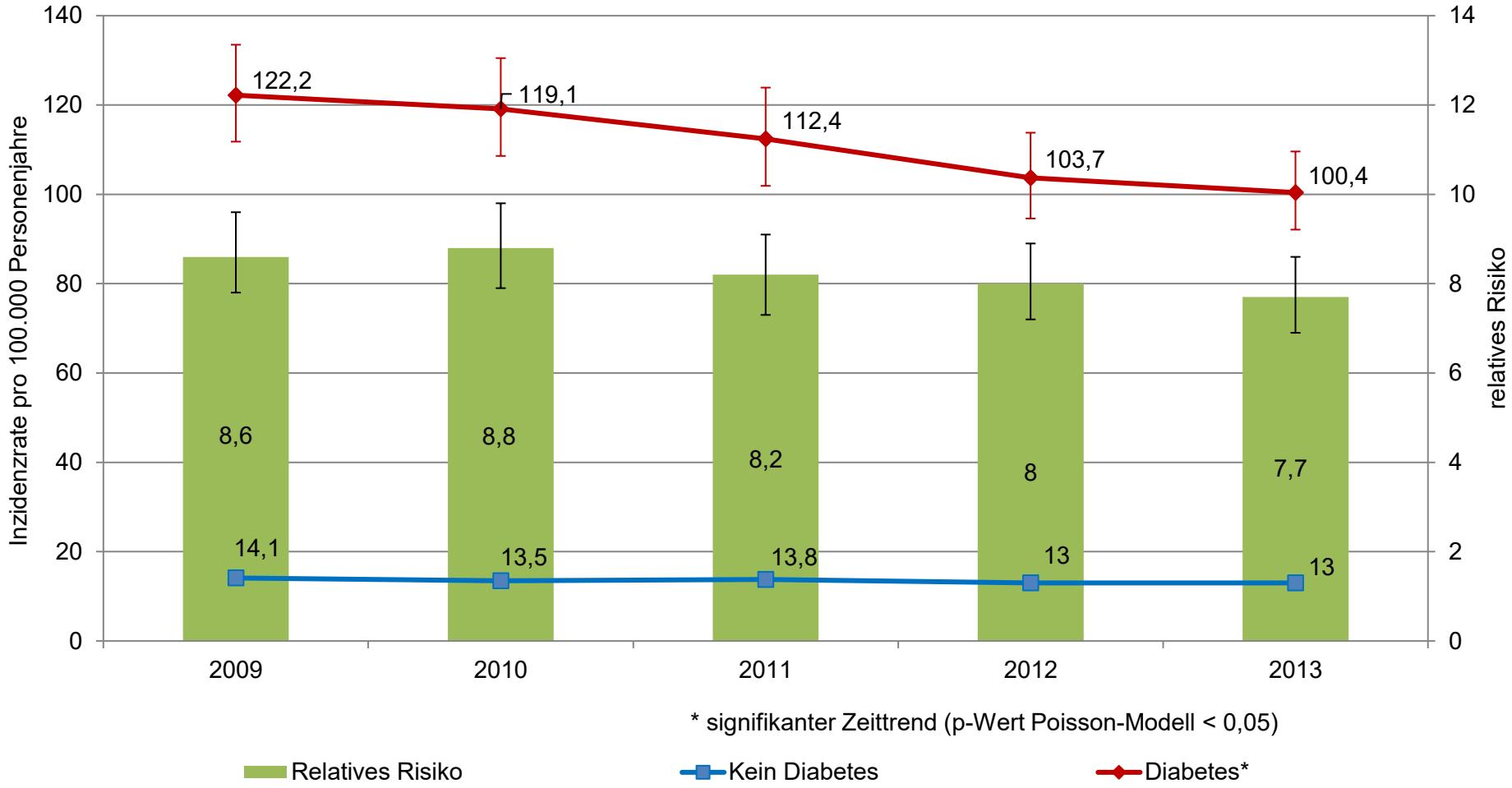
Eigen erstellte Abbildung

Abbildung 9: Inzidenzrate und relatives Risiko Minor-Amputation GKV-Daten 2008-2012



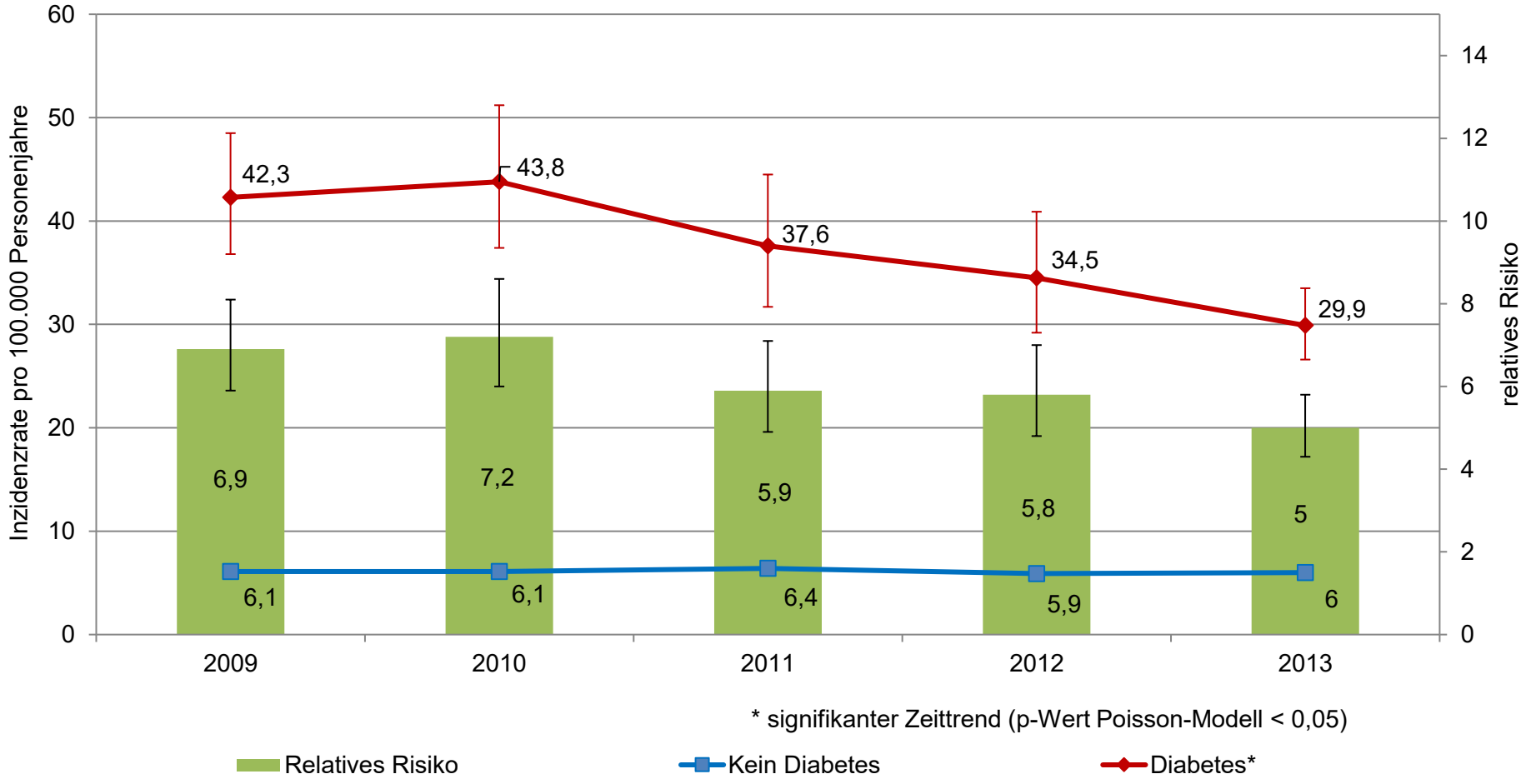
Eigen erstellte Abbildung

Abbildung 9: Inzidenzrate und relatives Risiko Amputationen (Major und Minor) Belgien 2009-2013



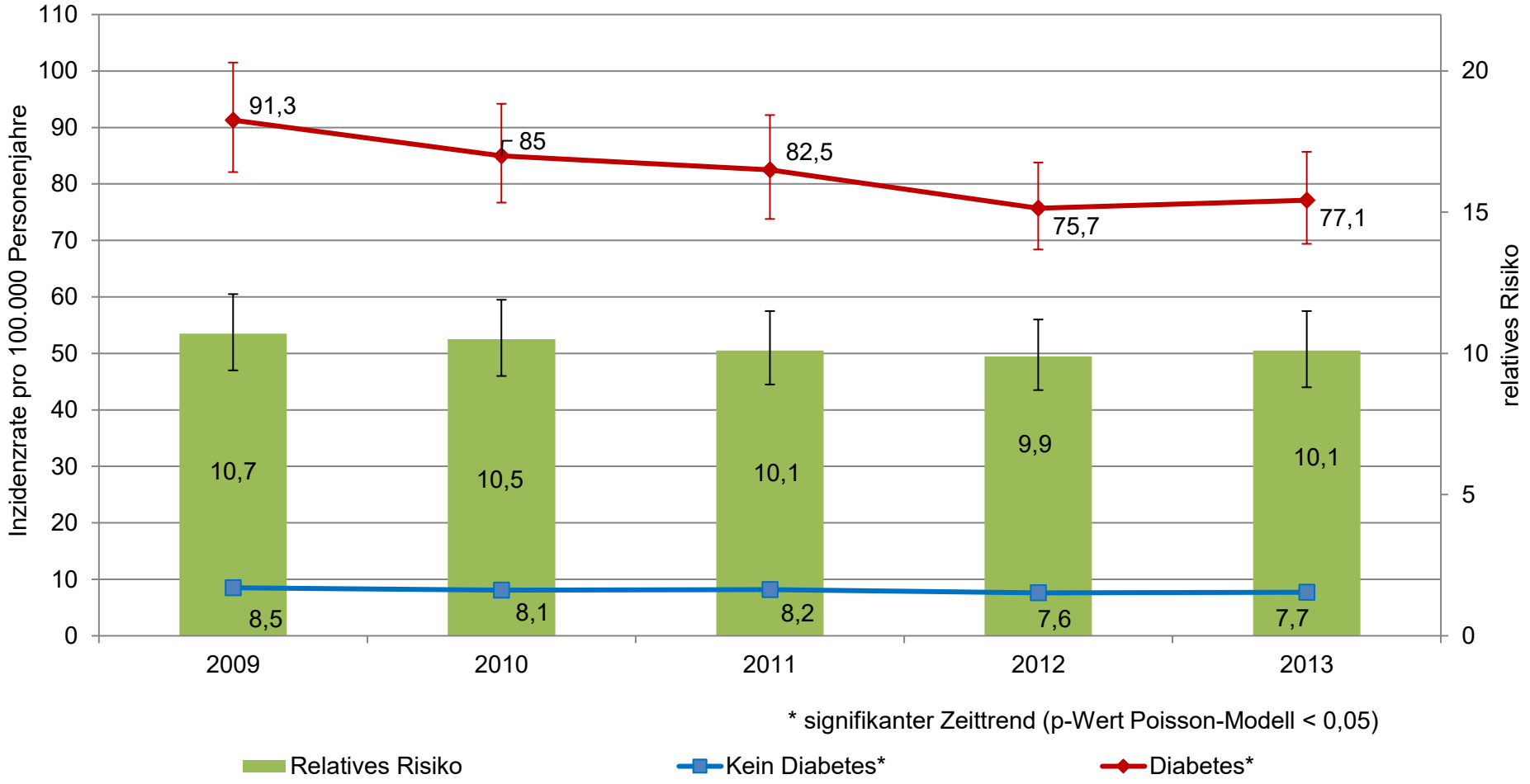
Eigen erstellte Abbildung

Abbildung 10: Inzidenzrate und relatives Risiko Major-Amputation Belgien 2009-2013



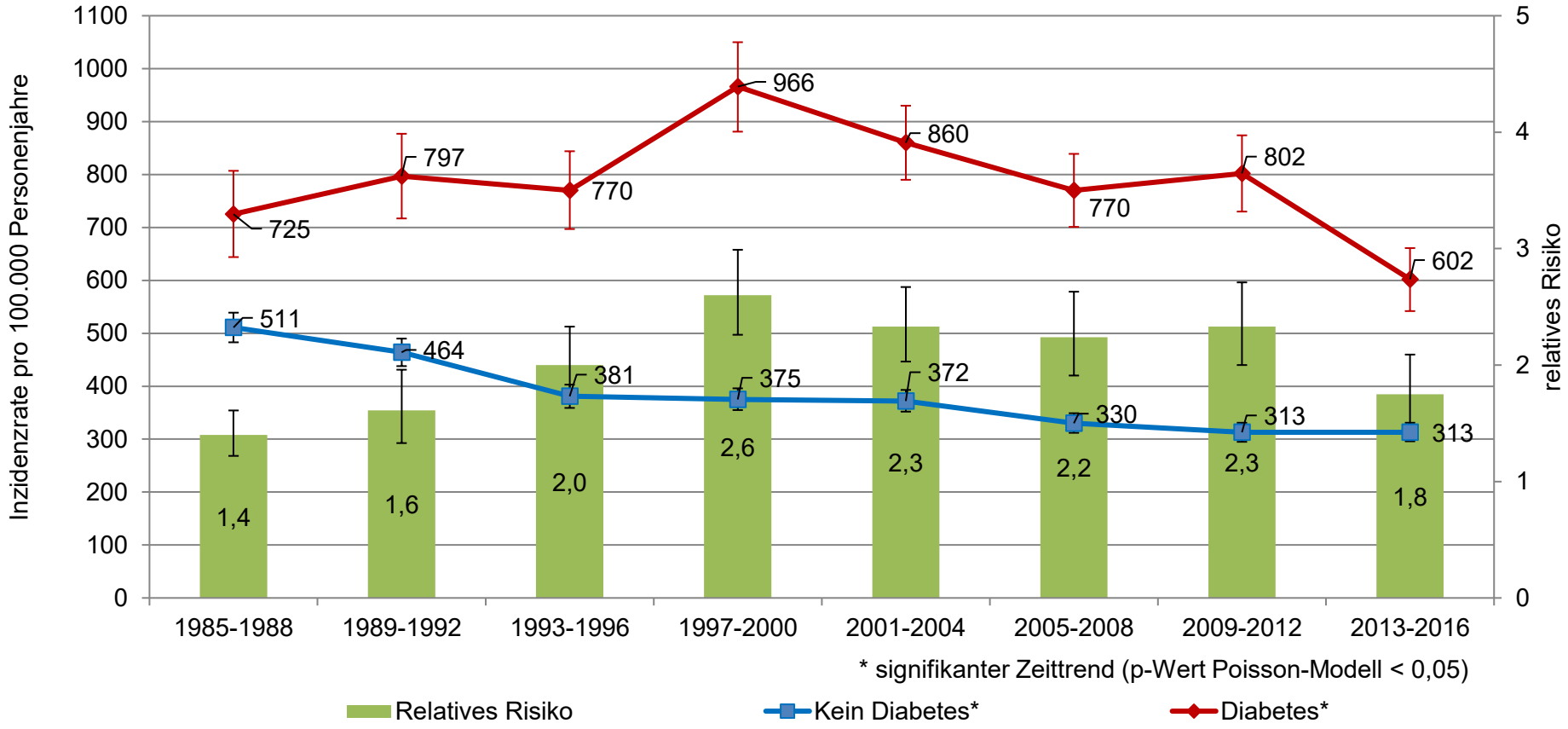
Eigen erstellte Abbildung

Abbildung 11: Inzidenzrate und relatives Risiko Minor-Amputation Belgien 2009-2013



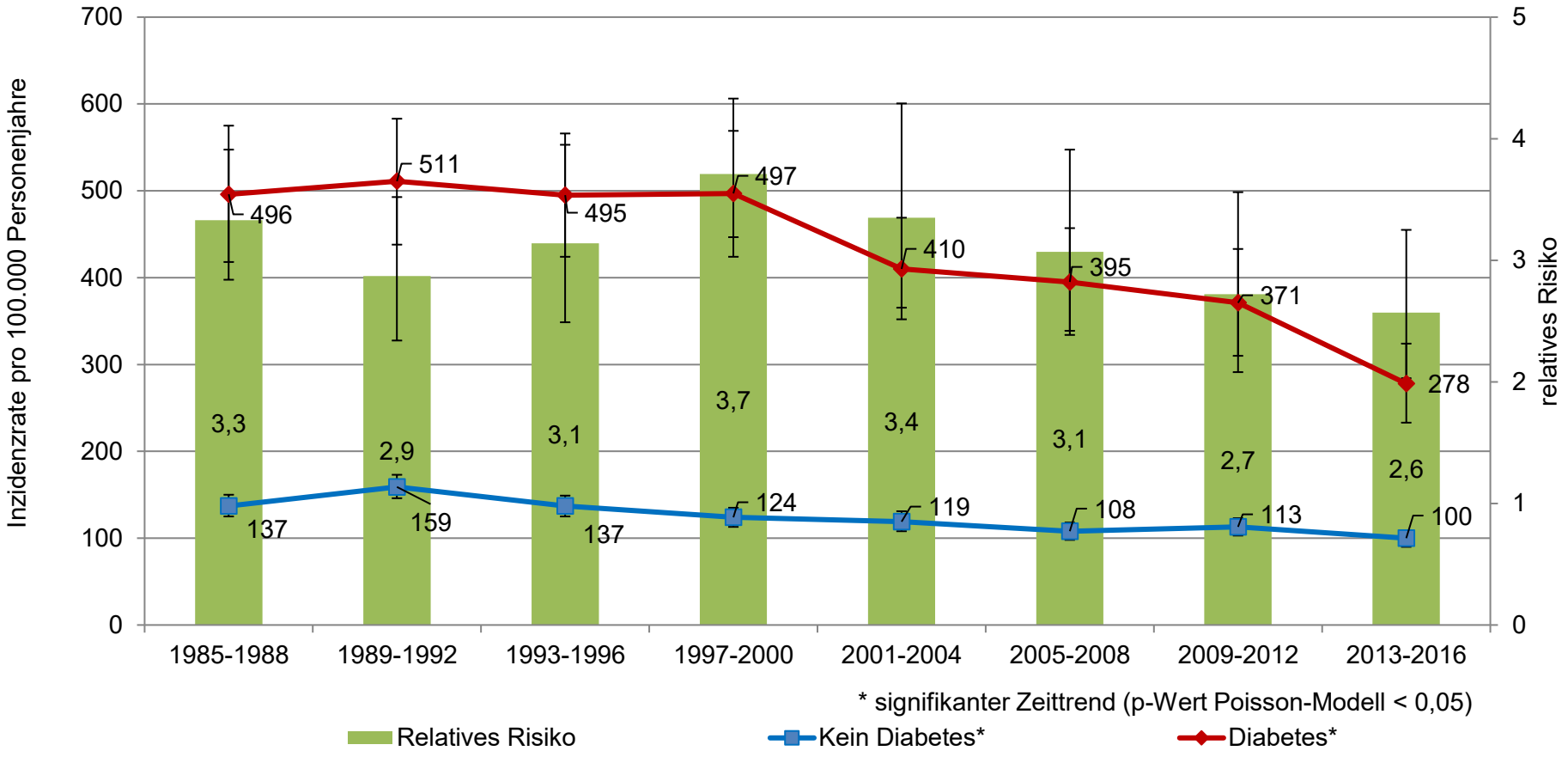
Eigen erstellte Abbildung

Abbildung 12: Inzidenzrate und relatives Risiko alle Herzinfarkte Männer 1985-2016



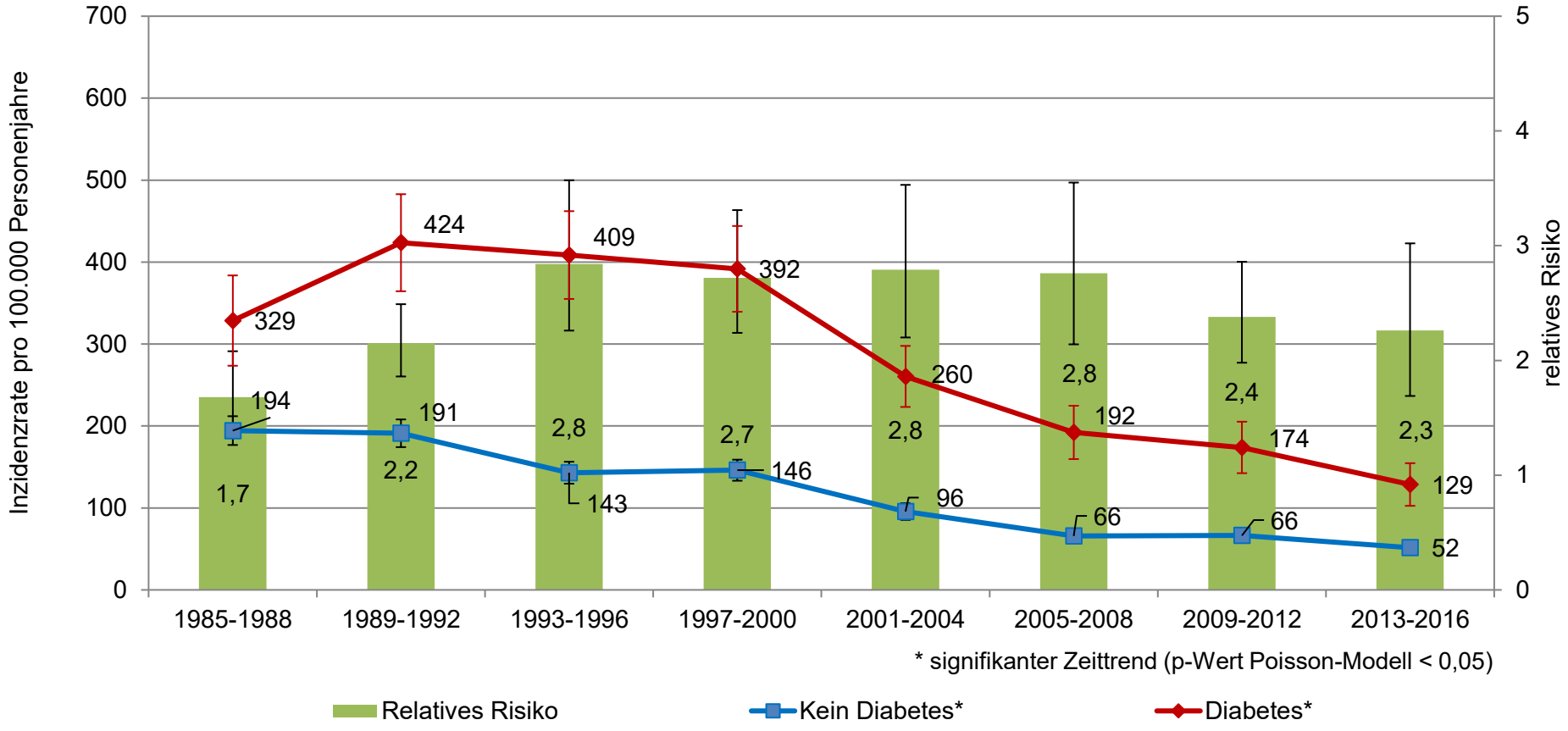
Eigen erstellte Abbildung

Abbildung 13: Inzidenzrate und relatives Risiko alle Herzinfarkte Frauen 1985-2016



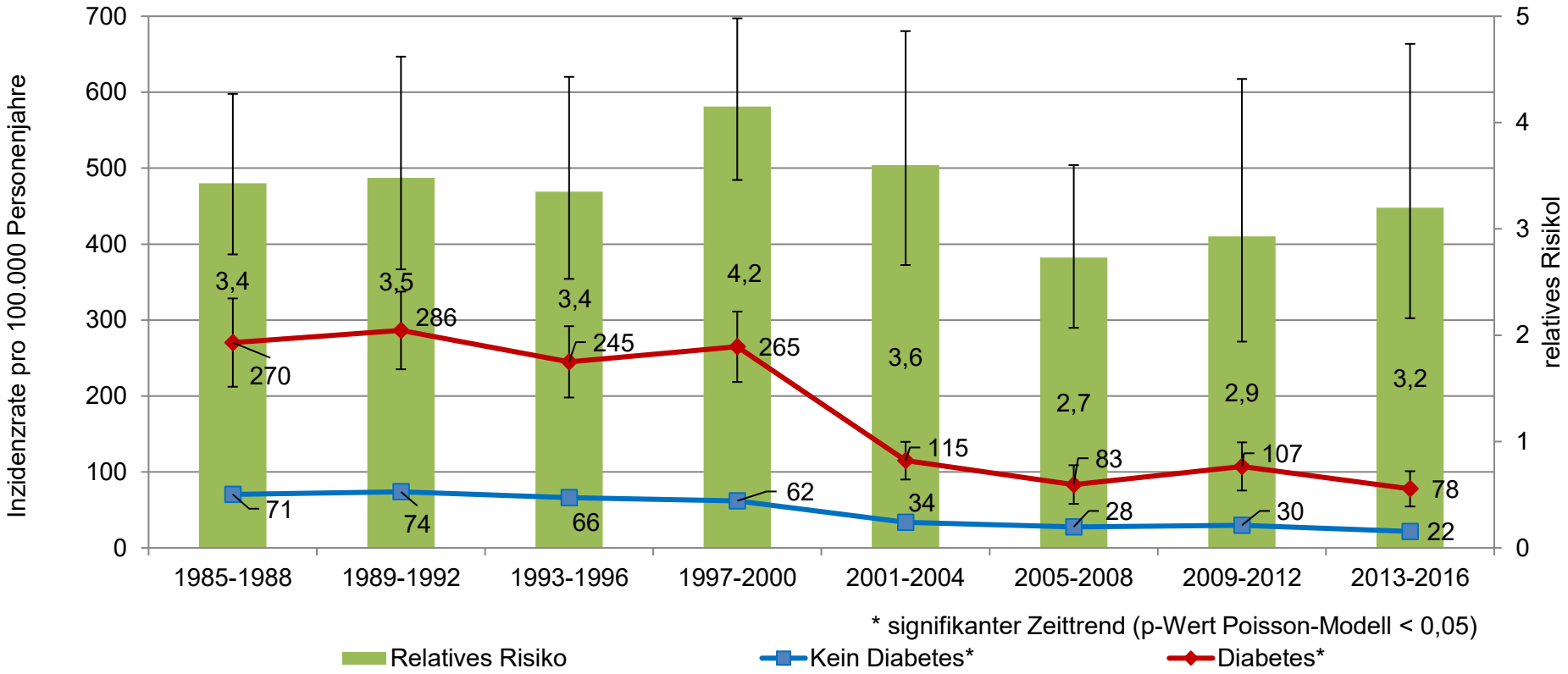
Eigen erstellte Abbildung

Abbildung 14: Inzidenzrate und relatives Risiko fatales Ereignis Männer 1985-2016



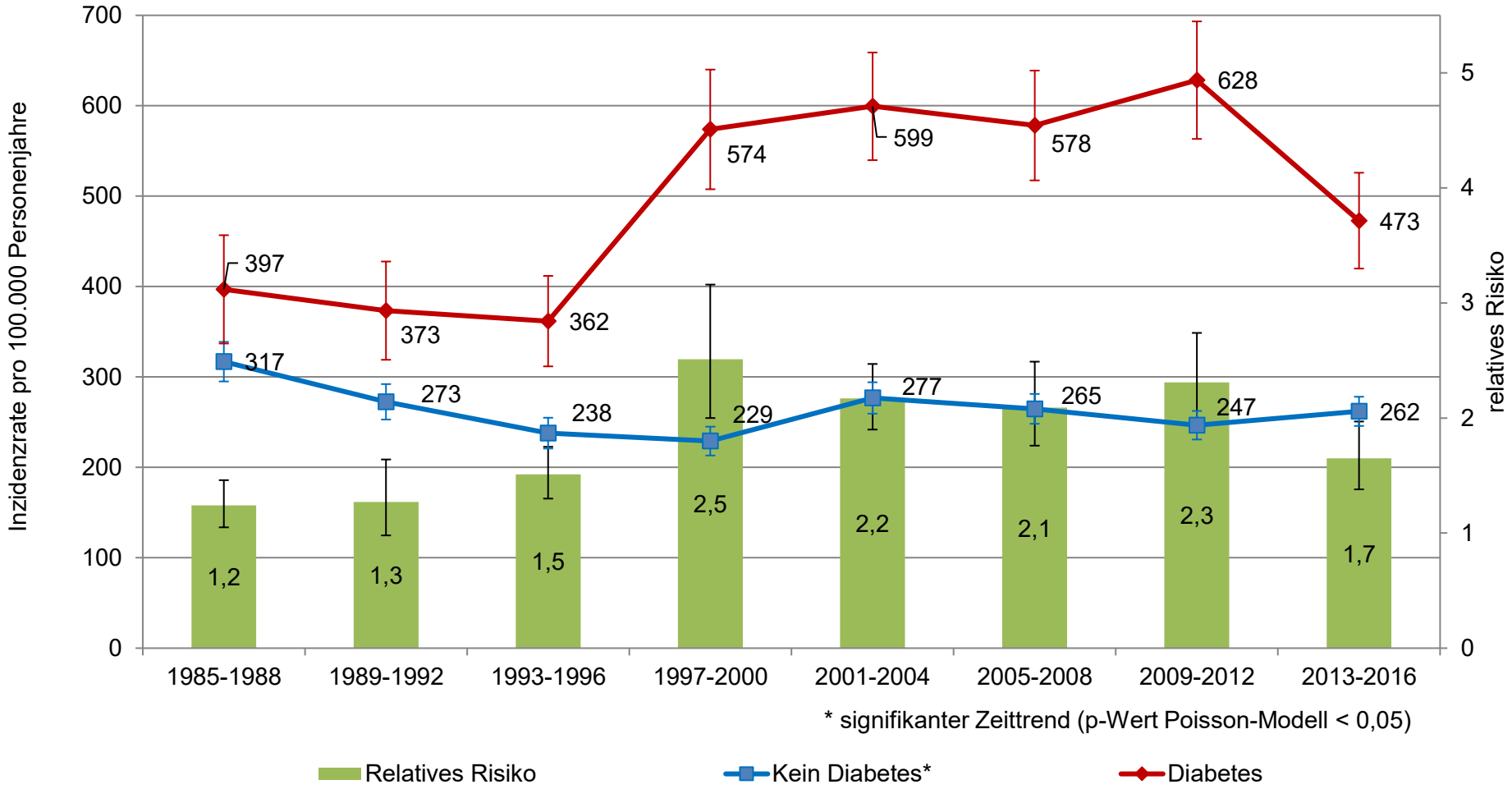
Eigen erstellte Abbildung

Abbildung 15: Inzidenzrate und relatives Risiko fatales Ereignis Frauen 1985-2016



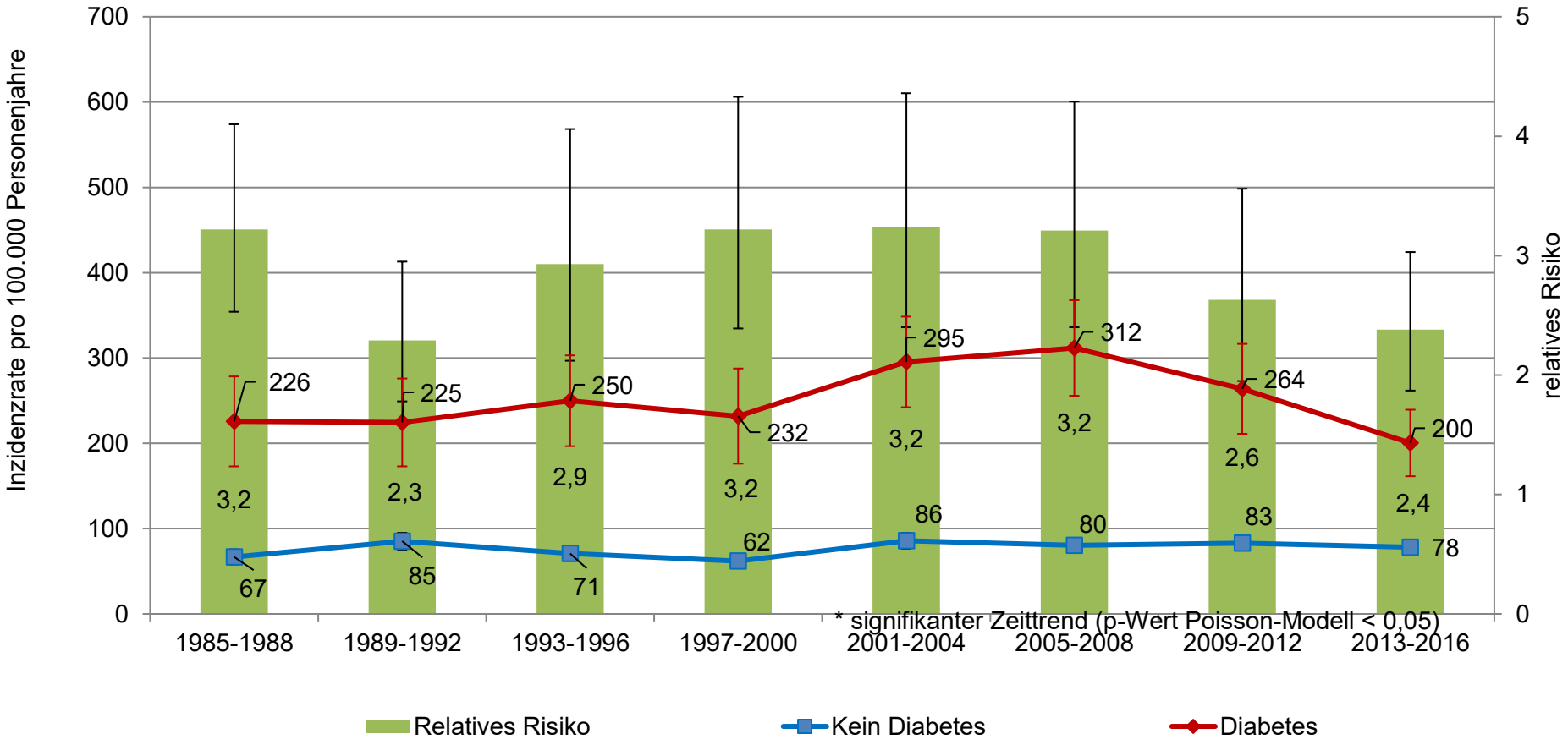
Eigen erstellte Abbildung

Abbildung 16: Inzidenzrate und relatives Risiko nicht-fataler Herzinfarkt Männer 1985-2016



Eigen erstellte Abbildung

Abbildung 17: Inzidenzrate und relatives Risiko nicht-fataler Herzinfarkt Frauen 1985-2016



Eigen erstellte Abbildung

Originalarbeit 1 (Titel: "Decreasing incidence of blindness in people with and without diabetes in southern Germany, 2008–2012.")

Die erste Originalarbeit untersuchte die altersadjustierte Inzidenzrate der Erblindung zwischen 2008 und 2012 für Personen mit und ohne Diabetes in 22 von 45 Landkreisen, bzw. kreisfreien Städten Baden-Württembergs anhand von Blindengeldempfängerdaten [Claessen et al. 2018]. Dabei bildeten die repräsentativen GEDA-Surveys der Jahre 2009, 2010 und 2012 Grundlage für eine erstmals repräsentative und zu mehreren Zeitpunkten während der Studie erfolgte Schätzung der diabetischen Bevölkerung.

Zwischen 2008 und 2012 sank die Erblindungsinzidenz in der Bevölkerung mit Diabetes deutlich um durchschnittlich 16 Prozent pro Jahr (relatives Risiko pro Kalenderjahr: 0,84, 95% KI: 0,78-0,90). In der Population ohne Diabetes war der Rückgang mit neun Prozent pro Jahr (0,91; 0,87-0,95), wenngleich etwas moderater, ebenfalls signifikant. Das Personen mit und ohne Diabetes vergleichende relative Risiko sank in der Beobachtungsperiode um neun Prozent pro Jahr von 1,9 in 2008 auf 1,3 in 2012 wobei der Rückgang nicht signifikant war (Änderung relatives Risiko pro Kalenderjahr: 0,91; 95% KI: 0,82-1,02).

Interessant war indes, dass das relative Risiko bei zunehmenden Alter sich deutlich verringerte und bei über 90-jährigen Personen sogar Menschen mit Diabetes eine geringere Erblindungsinzidenz aufwiesen. Die Ergebnisse waren bei Männer und Frauen sehr ähnlich, mit Ausnahme der Frauen mit Diabetes, bei denen der Rückgang der Inzidenzrate etwas stärker ausgeprägt war.

Verglichen mit der Erblindungsinzidenz aus den 90er Jahren ist die Inzidenzrate in der Bevölkerung mit Diabetes deutlich stärker zurückgegangen als bei Personen ohne Diabetes. Infolgedessen ist das Personen mit und ohne Diabetes vergleichende relative Risiko von 4.0 (95% KI: 3,0-5,3) in 1990 auf 1,3 (1,01-1,9) in 2012 merklich zurückgegangen.

Originalarbeit 2 (Titel: "Decreasing incidence of stroke in diabetic but not in the non-diabetic population: A community-based stroke register.")

Die zweite Originalarbeit untersuchte erstmals den zeitlichen Trend der altersadjustierten Schlaganfallinzidenz in Deutschland bei Personen mit und ohne Diabetes anhand des

Erlanger Schlaganfallregisters für den Zeitraum 1998 bis 2014 [Icks, Claessen et al. 2017]. Dabei war es zum ersten Mal möglich, Menschen mit unbekannten Diabetes zu erfassen und bei der Inzidenzschätzung zu berücksichtigen.

Die Schlaganfallinzidenz sank in der Bevölkerung mit Diabetes zwischen 1998 und 2014 signifikant um 1,5 Prozent pro Jahr (relatives Risiko pro Kalenderjahr: 0,985; 95% KI 0,972-0,9995) mit einem besonders deutlichen Rückgang in den letzten drei Jahren der Beobachtungsperiode. Im Gegensatz dazu war kein konsistenter Zeittrend der Schlaganfallinzidenz bei Personen ohne Diabetes zu erkennen, wobei es zu leichten Schwankungen der Inzidenzschätzung kam aufgrund der relativ geringen Anzahl an Schlaganfällen pro Jahr. Das Menschen mit und ohne Diabetes vergleichende relative Risiko ging signifikant um zwei Prozent pro Jahr zurück von 1,9 in 1998 auf 1,0 in 2014 (Änderung relatives Risiko pro Kalenderjahr: 0,979; 95% KI: 0,960-0,997).

Interessant war, dass der Rückgang der Schlaganfallinzidenz in der Bevölkerung mit Diabetes deutlich schwächer und nicht signifikant war, wenn nur ischämische Schlaganfälle gezählt wurden, obwohl dieser Subtyp etwa 85% aller Schlaganfälle im Erlanger Register ausmachte. In der Bevölkerung ohne Diabetes war auch hier kein konsistenter Zeittrend zu erkennen. Ebenso war hier kein einheitlicher Trend beim Personen mit und ohne Diabetes vergleichenden relativen Risiko zu erkennen. Dieses schwankte zwischen 2,6 (95% KI: 1,7-4,1) in 2001 und 1,0 (0,7-1,5) in 2014 (Änderung relatives Risiko pro Kalenderjahr: 0,987; 95% KI: 0,967-1,006).

Alle Ergebnisse bezüglich Schlaganfallinzidenz waren bei beiden Geschlechtern ähnlich mit dem einzigen Unterschied, dass die Inzidenzraten bei Männern etwa um den Faktor 1,25 höher waren. Die Sensitivitätsanalysen zeigten, dass die Ergebnisse nahezu identisch blieben unter der Annahme, dass sich die Diabetesprävalenz ab 2011 als konstant darstellt. Ebenso hatte das Zählen der Personen mit Schlaganfall und unbekanntem Diabetesstatus als Menschen mit Diabetes bzw. ohne Diabetes keinen wesentlichen Einfluss auf die Ergebnisse.

Originalarbeit 3 (Titel: "Incidence and relative risk of renal replacement therapy in people with and without diabetes between 2002 and 2016 in a German region.")

In der dritten Originalarbeit erfolgte erstmals die Untersuchung des zeitlichen Trends der altersadjustierten RRT-Inzidenzrate in der Bevölkerung mit und ohne Diabetes in Deutschland mit Hilfe der Daten aus den Dialysezentren im Kreis Mettmann für den Zeitraum 2002 und 2016 betreffend alle Personen ab 30 Jahre [Narres, Claessen et al. 2019]. Vergleichbar mit der Arbeit zum Schlaganfall war es zum ersten Mal möglich, mit Hilfe der bundesweiten repräsentativen BGS und DEGS Surveys die Diabetesprävalenz dynamisch zu schätzen und gleichzeitig den unbekannten Diabetes zu berücksichtigen.

Aufgrund der relativ geringen Anzahl an erster RRT pro Jahr gab es leichte Schwankungen in der Inzidenzschätzung. Dabei lag die RRT-Inzidenzrate bei der Bevölkerung mit Diabetes bei 93,6 pro 100.000 PJ (95% KI: 50,4-136,7) in 2002 und 140,5 (80,6-200,4) in 2016. Die Inzidenzrate bei Personen ohne Diabetes war deutlich niedriger und lag bei 17,3 (10,9-23,6) in 2002 und 24,6 (17,5-31,7) in 2016. Ein konsistenter Zeittrend der RRT-Inzidenzrate konnte weder in der Bevölkerung mit noch ohne Diabetes beobachtet werden, wobei sich ähnliche Resultate bei beiden Geschlechtern ergaben mit dem einzigen Unterschied, dass die Inzidenzraten bei Männern etwa doppelt so hoch waren im Vergleich zu denen der Frauen. Infolgedessen blieb auch das Personen mit und ohne Diabetes vergleichende relative Risiko nahezu unverändert mit einem durchschnittlichen Wert von 4,5 (Änderung relatives Risiko pro Kalenderjahr: 0,98; 95% KI: 0,95-1,02).

Wenn nur Personen mit diabetischer Nephropathie als Ursache für die RRT-Inzidenzrate gezählt wurden, war ein moderater Rückgang der Inzidenzrate erkennbar, welcher allerdings nur bei den Männern signifikant war mit vier Prozent pro Jahr (relatives Risiko pro Kalenderjahr: 0,96; 0,93-0,997).

Analog zum Schlaganfall zeigten auch hier die Sensitivitätsanalysen, dass die Ergebnisse nahezu identisch blieben unter der Annahme einer konstanten Diabetesprävalenz ab 2011.

Originalarbeit 4 (Titel: "Renal replacement therapy in people with and without diabetes in Germany, 2010–2016: an analysis of more than 25 million inhabitants.")

Die vierte Originalarbeit verknüpfte Daten der gesetzlichen Krankenkassen AOK und BKK zu einem Datenpool von etwa 25 Millionen Versicherten, so dass die Schätzung des zeitlichen Trends der altersadjustierten RRT-Inzidenzrate bei Menschen mit und ohne Diabetes in Deutschland erstmals in einem deutlich größeren und repräsentativeren Kollektiv möglich war [Claessen, Narres et al. 2021]. Dabei konnte die Operationalisierung der RRT insbesondere durch Berücksichtigung der Diagnose N18.5 („Chronische Nierenkrankheit, Stadium 5") deutlich verbessert werden. Darüber hinaus konnte der zeitliche Trend der RRT-Inzidenzrate nicht nur geschlechtsstratifiziert, sondern erstmals in Deutschland auch getrennt für Altersgruppen in 10 Jahresschritten analysiert werden.

Die RRT-Inzidenzrate war in der Bevölkerung mit Diabetes mit 114,1 pro 100.000 PJ (95% KI: 110,0-117,2). Sie war damit etwa sechsmal so hoch im Vergleich zur Inzidenzrate in der Population ohne Diabetes mit 19,6 (19,4-19,8). Der zeitliche Verlauf der RRT-Inzidenzrate war bei Männer und Frauen gut vergleichbar. Sie unterschieden sich lediglich darin, dass Männer unabhängig vom Diabetesstatus eine etwa doppelt so hohe RRT-Inzidenzrate aufwiesen. In der Bevölkerung mit Diabetes war ein signifikanter Rückgang der RRT-Inzidenzrate um etwa drei Prozent pro Jahr (relatives Risiko pro Kalenderjahr: 0,972; 95% KI: 0,965-0,979) zu erkennen. Dieser Rückgang war konsistent sowohl bei Männer und Frauen sowie unabhängig vom Alter zu erkennen. Interessant war, dass kein Rückgang in der Population ohne Diabetes beobachtet werden konnte außer bei Männer und Frauen über 80 Jahre sowie bei Frauen unter 40 Jahren. Das Personen mit und ohne Diabetes vergleichende relative Risiko verringerte sich nur moderat aber nicht signifikant um zwei Prozent pro Jahr von 6,3 in 2010 auf 5,4 in 2016 (Änderung relatives Risiko pro Kalenderjahr: 0,98; 95% KI: 0,95-1,02).

Originalarbeit 5 (Titel: "Lower-extremity amputations in people with and without diabetes in Germany, 2008–2012—an analysis of more than 30 million inhabitants. Clinical Epidemiology.")

In der fünften Originalarbeit erfolgte ebenfalls die Verknüpfung von Daten der gesetzlichen Krankenkassen BARMER GEK, AOK und BKK zu einem deutlich größeren und repräsentativeren Datenpool, mehr als ein Drittel der deutschen Gesamtbevölkerung

inkludierend [Claessen et al. 2019]. Dem Problem der Linkszensierung bei Amputationen in Krankenkassendaten konnte erstmals entgegengewirkt werden durch die Schätzung von altersadjustierten Amputationsraten für jedes Kalenderjahr ungeachtet dessen, ob Amputationen in früheren Jahren stattfanden.

Zwischen 2008 und 2012 sank die Amputationsinzidenz bei Personen mit Diabetes signifikant um vier Prozent pro Jahr (relatives Risiko pro Kalenderjahr: 0,96; 95% KI: 0,95-0,96). Die Amputationsinzidenz blieb in der Bevölkerung ohne Diabetes im Gegensatz zur Population mit Diabetes nahezu konstant. Daher ging das relative Risiko zwischen beiden Populationen signifikant um drei Prozent pro Jahr von 9,3 in 2008 auf 8,1 in 2012 zurück (Änderung relatives Risiko pro Kalenderjahr: 0,97; 95% KI: 0,95-0,99).

Der Rückgang der Amputationsinzidenz bei Personen mit Diabetes war besonders deutlich, wenn nur Major-Amputationen gezählt wurden. Hierbei war ein Rückgang von 9% pro Jahr zu erkennen (relatives Risiko pro Kalenderjahr 0,91; 95% KI: 0,90-0,92). Hervorzuheben ist, dass hier auch eine signifikante Reduktion um sechs Prozent pro Jahr (0,94; 0,92-0,96) in der Bevölkerung ohne Diabetes zu beobachten war. Aufgrund des stärkeren Rückgangs in der Bevölkerung mit Diabetes reduzierte sich das relative Risiko signifikant um vier Prozent pro Jahr von 5,7 in 2008 auf 5,1 in 2012 (Änderung relatives Risiko pro Kalenderjahr: 0,96; 95% KI: 0,94-0,98).

Wenn nur Minor-Amputationen gezählt wurden sank die Amputationsinzidenz dagegen deutlich moderater mit 3% pro Jahr in der Bevölkerung mit Diabetes (relatives Risiko pro Kalenderjahr: 0,97; 95% KI: 0,96-0,98). Bemerkenswert war, dass diese Zahl in der Population ohne Diabetes sogar, wenngleich moderat, signifikant um 2 Prozent pro Jahr (1,02; 1,001-1,04) zunahm. Infolge der divergenten Zeittrends in den Bevölkerungen mit und ohne Diabetes sank das relative Risiko signifikant um fünf Prozent pro Jahr von 13,1 in 2008 auf 10,4 in 2012 (Änderung relatives Risiko pro Kalenderjahr: 0,95; 95% KI: 0,94-0,97).

Die Ergebnisse waren bei beiden Geschlechtern vergleichbar. Einzige Unterschiede waren, dass die Amputationsinzidenz bei den Männern in allen Subgruppen rund 2,5-mal höher als

bei den Frauen und der Rückgang der Amputationsinzidenz bei den Frauen mit Diabetes etwas stärker ausgeprägt war.

Originalarbeit 6 (Titel: "Decreasing rates of lower-extremity amputation in people with and without diabetes in Belgium: a nationwide study.")

Die sechste Originalarbeit untersuchte die altersadjustierte Amputationsinzidenz in Belgien mit Krankenkassendaten für den Zeitraum 2009 bis 2013, wobei erstmals eine fast vollständige Bevölkerung eines Landes eingeschlossen werden konnte [Claessen et al. 2018].

Zwischen 2009 und 2013 sank die Amputationsinzidenz in der Bevölkerung mit Diabetes signifikant um fünf Prozent pro Jahr (relatives Risiko pro Kalenderjahr:0,95; 95% KI: 0,94-0,95). Diese Zahl ging ebenfalls, wenngleich moderater, bei Personen ohne Diabetes mit zwei Prozent pro Jahr (0,98; 0,97-0,99) zurück. Entsprechend sank das die Personen mit und ohne Diabetes vergleichende relative Risiko in diesem Zeitraum signifikant um drei Prozent pro Jahr von 8,6 auf 7,7 (Änderung relatives Risiko pro Kalenderjahr: 0,965; 95% KI: 0,944-0,985).

Wie in der Originalarbeit mit deutschen Daten war auch hier der Rückgang der Amputationsinzidenz in der Bevölkerung mit Diabetes besonders stark, wenn nur Major-Amputationen gezählt wurden. So sank diese Zahl signifikant um acht Prozent pro Jahr im Beobachtungszeitraum (relatives Risiko pro Kalenderjahr 0,92; 95% KI: 0,91-0,93). Interessant war hier, dass in der Bevölkerung ohne Diabetes anders als in Deutschland kein Rückgang der Major-Amputationsinzidenz zu erkennen war. Das Personen mit und ohne Diabetes vergleichende relative Risiko verminderte sich entsprechend signifikant um sieben Prozent pro Jahr von 6,9 auf 5,0 (Änderung relatives Risiko pro Kalenderjahr: 0,93; 95% KI: 0,91-0,95).

Die hier zusätzlich unternommene Unterscheidung zwischen Major-Amputationen oberhalb und unterhalb des Knies ergab, dass der Rückgang der oberhalb des Knies-Major-Amputationsinzidenz in der Bevölkerung mit Diabetes mit zehn Prozent pro Jahr besonders stark war (relatives Risiko pro Kalenderjahr 0,90; 95% KI: 0,89-0,92). Bei Major-Amputationen unterhalb des Knies betrug dieser Wert lediglich sieben Prozent pro Jahr (0,93; 0,91-0,94). Bemerkenswert erscheint, dass bei den Personen ohne Diabetes ein signifikanter Rückgang um vier Prozent zu erkennen war (0,96; 0,94-0,98), wenn Major-Amputationen unterhalb des

Knies gezählt wurden, während sich kein zeitlicher Trend bei Major-Amputationen oberhalb des Knies erkennen ließ.

Wie schon in den deutschen Daten war auch hier der Rückgang der Amputationsinzidenz in der Bevölkerung mit Diabetes moderater, wenn nur Minor-Amputationen gezählt wurden. So sank die Minor-Amputationsinzidenz in der Population mit Diabetes signifikant um fünf Prozent pro Jahr (relatives Risiko pro Kalenderjahr 0,95; 95% KI: 0,94-0,96). Bemerkenswert war wiederum, dass im Gegensatz zu den deutschen Daten hier auch die Minor-Amputationsinzidenz bei Menschen ohne Diabetes, wenngleich moderat, aber signifikant um drei Prozent pro Jahr (0,97; 0,95-0,99) zurückging. Entsprechend blieb das Menschen mit und ohne Diabetes vergleichende relative Risiko nahezu unverändert im Beobachtungszeitraum um den Faktor zehn (Änderung relatives Risiko pro Kalenderjahr: 0,98; 95% KI: 0,96-1,003).

Wie in den deutschen Daten waren auch hier die Ergebnisse bezüglich des zeitlichen Trends bei beiden Geschlechtern relativ gut vergleichbar. Allerdings war der Rückgang der Major-Amputationsinzidenz bei Frauen mit Diabetes etwas stärker ausgeprägt. Auch bei den Minor-Amputationen von Männern mit und ohne Diabetes ergab sich ein etwas stärkerer Rückgang.

Wesentlichster Unterschied war, dass die Amputation-Inzidenzraten bei den Männern in allen Subgruppen etwa doppelt so hoch wie bei den Frauen waren.

Sich im Einreichungsprozess befindende Arbeit (Titel: "Incidence and relative risk of myocardial infarction in people with and without diabetes between 1985 and 2016 in a German region.")

Das Ziel der sich im Einreichungsprozess befindenden Arbeit ist es die altersadjustierte Herzinfarktinzidenz in der Region Augsburg über einen deutlich längeren Beobachtungszeitraum und unter Berücksichtigung von fatalen und nicht fatalen Ereignissen zu untersuchen. Dabei kam erstmals die Schätzung der diabetischen Bevölkerung über ZI-Daten zur Anwendung, welche die Diabetesprävalenz im Zeitraum 2009-2016 deutlich repräsentativer und valider schätzen als die KORA-Surveys.

Im Gegensatz zu den meisten anderen mit Diabetes assoziierten Komplikationen waren die Ergebnisse bezüglich des zeitlichen Trends bei Männer und Frauen sehr unterschiedlich.

Die Inzidenzrate eines Herzinfarktes war über den gesamten Beobachtungszeitraum in der Bevölkerung mit Diabetes mit 572 pro 100.000 PJ etwa doppelt so hoch wie bei Personen ohne Diabetes (relatives Risiko: 1,96; 95% KI: 1;89-2,03). Dabei war die Inzidenzrate bei Männern unabhängig vom Diabetesstatus deutlich höher als bei Frauen (Inzidenzrate Männer mit Diabetes: 744; Frauen mit Diabetes: 416; Männer ohne Diabetes 380; Frauen ohne Diabetes: 120). Die Inzidenzrate des ersten Herzinfarktes stieg in der männlichen Bevölkerung mit Diabetes bis zum Jahr 2000 an und sank danach mit einem signifikanten Rückgang in der letzten Zeitperiode 2013-2016. Dagegen bewegte sich diese Zahl bei Frauen mit Diabetes sowie Frauen ohne Diabetes bis Anfang der 2000er auf einem Plateau und sank danach deutlich. Bei Männer ohne Diabetes wiederum sank diese Zahl kontinuierlich bereits in den späten 1980er Jahren. Betreffend des Personen mit und ohne Diabetes vergleichenden relativen Risikos war bei Frauen kein konsistenter Trend zu erkennen, wobei das relative Risiko durchweg um den Faktor drei lag. Dagegen stieg diese Zahl bei Männern von 1,40 (95% KI: 1,22-1,61) in 1985-1988 auf 2,60 (2,26-2,99) in 1997-2000 an und ging danach auf 1,75 (1,47-2,09) in 2013-2016 zurück.

Bezüglich fataler Ereignisse sank die Inzidenzrate mit einem besonders starken Rückgang nach dem Jahr 2000 unabhängig von Geschlecht und Diabetesstatus. Hier imponierte, dass bei Männern ohne Diabetes der Rückgang früher zu erkennen war als bei Männern mit Diabetes. Deswegen stieg das relative Risiko bei Männern deutlich an von 1,68 (95% KI: 1,35-2,08) in 1985-1988 auf 2,84 (2,26-3,57) in 1997-2000 und sank danach auf 2,26 (1,69-3,02) in 2013-2016. Das Personen mit und ohne Diabetes vergleichende relative Risiko zeigte auch hier keinen konsistenten Zeittrend bei Frauen mit Werten zwischen drei und vier.

Die Inzidenzrate nicht fataler Herzinfarkte stieg interessanterweise bei Männern mit Diabetes bis zur Zeitperiode 2009-2012 an und sank lediglich in 2013-2016. Dagegen war kein konsistenter Zeittrend zu erkennen bei Frauen mit Diabetes sowie Männer und Frauen ohne Diabetes. Ebenso war betreffend das relative Risiko bei Frauen kein eindeutiger Zeittrend zu erkennen. Im Gegensatz dazu stieg diese Zahl bei Männern deutlich an von 1,24 (95% KI:

1,05-1,46) in 1985-1988 auf 2,51 in (2,00-3,16) 1997-2000 mit einem fast ebenso klaren Rückgang danach auf 1,65 (1,38-1,97) in 2013-2016.

5. Gesamtdiskussion

5.1 Zusammenfassung der wichtigsten Ergebnisse

Die in dieser Schrift zusammengefassten Arbeiten erweitern durch ihre Ergebnisse den Stand der Forschung zum zeitlichen Trend der Inzidenzrate von mit Diabetes assoziierten Komplikationen bei Menschen mit und ohne Diabetes. Dies beruht im Hinblick auf die zuvor gegebene Studienlage auf Verbesserungen in Methodik und Datenbasis, die sich im Wesentlichen in sechs Aspekte aufgliedern lassen.

Die erste Verbesserung betrifft die Verlängerung des Beobachtungszeitraumes. Hierdurch wurde insbesondere bei Schlaganfall und RRT in Deutschland eine erstmalige Untersuchung des zeitlichen Trends über mehr als eine Dekade ermöglicht. Auch mit Rückgriff auf die Krankenkassendaten konnte sowohl in Deutschland wie in Belgien eine Verbesserung der Forschung erzielt werden, ermöglichte auch dies erstmals die Untersuchung des zeitlichen Trends.

Die zweite große Verbesserung war die deutlich validere Schätzung der Bevölkerung mit Diabetes. Bei den Originalarbeiten mit populationsbasierten Registerdaten (betreffend Erblindung, Schlaganfall, Herzinfarkt sowie RRT) erfolgte die Diabetesprävalenzschätzung erstmals über repräsentative bundesweite Surveys zu verschiedenen Zeitpunkten während der Studienperiode. Durchgreifender Vorteil dieser Methode war, dass hierdurch die zeitliche Veränderung der Diabetesprävalenz berücksichtigt werden konnte. In den Originalarbeiten mit Krankenkassendaten konnten erstmals Menschen mit während des Beobachtungszeitraums neu festgestelltem Diabetes in der Schätzung der Bevölkerung mit Diabetes berücksichtigt werden.

Drittens verbesserten die Forschungsarbeiten die vollständige und detailliertere Erfassung der mit Diabetes assoziierten Komplikationen. So konnte z.B. mit Hilfe von Registerdaten beim Schlaganfall erstmals in Deutschland auch fatale Schlaganfälle berücksichtigt werden. Außerdem war es nun möglich die Analyse unter Berücksichtigung der Subtypen des Schlaganfalls (Ischämischer und hämorrhagischer Schlaganfall) durchzuführen. Bei der sich im Einreichungsprozess befindenden Arbeit konnte erstmals der zeitliche Trend der Herzinfarkt-Inzidenz stratifiziert nach fatalen und nicht-fatalen Ereignissen durchgeführt werden. In Deutschland fand zum ersten Mal eine Untersuchung des zeitlichen Trends der Amputationsinzidenz sowohl für Major- als auch für Minor-Amputationen in den Populationen mit und ohne Diabetes statt. Hinzu kommt, dass in Belgien erstmals Major-Amputationen separat bezüglich Ebene der Major-Amputationen d.h. unterhalb und oberhalb des Knies untersucht werden konnten. Eine Verbesserung gegenüber vielen internationalen Forschungsarbeiten war ferner die nahezu vollständige Erfassung der untersuchten Komplikationen bei Menschen mit Diabetes unabhängig davon, ob Diabetes die Ursache der Komplikation war.

Eine vierte Verbesserung betraf den Umgang mit Linkszensierung in Krankenkassendaten, früher stattgefundene Amputation zu erfassen. Hier konnte erstmals die systematische Überschätzung der Inzidenzrate am Anfang des Beobachtungszeitraums ausgeglichen werden, indem für jedes Jahr ungeachtet von Vorereignissen eine Ereignisrate geschätzt wurde.

Fünftens war eine Verbesserung im Vergleich zu vielen internationalen Arbeiten, dass alle hier präsentierten Originalarbeiten den Alters- und Geschlechtseffekt bei der Inzidenzschätzung durch die Methode der direkten Standardisierung mit der geeigneten Wahl einer Standardpopulation berücksichtigt haben. Weiterhin konnten zeitliche Trends mit alters- und geschlechtsadjustierten Poisson-Regressionsmodellen untersucht werden. Darüber hinaus erfolgte erstmals eine nach Altersgruppen und Geschlecht getrennte Untersuchung des zeitlichen Trends, welche mit Krankenkassendaten bezüglich der RRT durchgeführt wurde.

Sechstens konnte die Studienpopulation deutlich vergrößert und repräsentativer gestaltet werden. So war es insbesondere bei Amputation und RRT erstmals möglich, in nationenweiten Populationen den zeitlichen Trend bei Menschen mit und ohne Diabetes zu analysieren. Dabei erfolgte die Untersuchung der Amputationsinzidenz in Belgien sogar anhand Daten von der nahezu vollständigen Bevölkerung. Eine Fortentwicklung im Vergleich zur vielen internationalen Forschungsarbeiten war zudem eine systematische Erfassung der mit Diabetes assoziierten Komplikationen über eine deutlich breitere Altersrange.

Die präsentierten Arbeiten untersuchten auf Basis von Krankenkassendaten und populationsbezogenen Registerdaten die zeitlichen Trends von Erblindung, Schlaganfall, Amputation, RRT als Marker für terminale Niereninsuffizienz sowie Herzinfarkt. Es zeigte sich insgesamt eine Reduktion der altersadjustierten Inzidenzraten aller genannten Komplikationen bei Menschen mit Diabetes, die insbesondere in den 2010er Jahren deutlich war. Dagegen war in der Bevölkerung ohne Diabetes ein entsprechender Rückgang deutlich moderater oder gar nicht vorhanden. Lediglich bei Erblindung, fatalen Ereignissen und Major-Amputation war in dieser Personengruppe ebenfalls ein deutlicher Rückgang zu verzeichnen. Überraschend war, dass die Inzidenzrate bei Minor-Amputationen in Deutschland in den 2010er Jahren sogar anstieg. Insgesamt sank in der Folge das relative Risiko in den meisten vorliegenden Forschungsarbeiten insbesondere in den 2010er Jahren. Eine wirklich merkliche Reduktion des relativen Risikos zwischen Menschen mit und ohne Diabetes war allerdings nur in den Forschungsarbeiten zu Amputation und Schlaganfall zu erkennen. Bei allen mit Diabetes assoziierten Komplikationen war die Inzidenzrate in der Bevölkerung mit Diabetes selbst am Ende der Beobachtungsperiode in den 2010er Jahren immer noch deutlich höher als in der Bevölkerung ohne Diabetes. Das relative Risiko wies bei Amputationen trotz des deutlichen Rückgangs am Ende mit Faktor acht bzw. Faktor fünf bei Major-Amputation, bzw. Faktor zehn bei Minor-Amputation immer noch den höchsten Wert von allen mit Diabetes assoziierten Komplikationen auf.

5.2 Vergleich mit bisherigen Forschungsarbeiten und Erklärungsansätze

Im Vergleich zu früheren nationalen sowie – soweit ersichtlich – den meisten internationalen Forschungsarbeiten war insgesamt ein deutlicher Rückgang der Inzidenzrate der aller hier untersuchten, mit Diabetes assoziierten Komplikationen zu erkennen.

So war der ermittelte Rückgang bei Erblindungen mit 16 Prozent pro Jahr deutlich stärker als in der Arbeit aus den 90er-Jahren, wo diese Zahl nur um 3 Prozent pro Jahr zurückging [Trautner et al. 2001].

Auch bzgl. Schlaganfall war ein Rückgang der Inzidenzrate – allerdings im Gegensatz zu den Forschungsarbeiten aus Schweden und Spanien – für Männer und Frauen mit Diabetes zu erkennen [Rautio et al. 2008, Munoz-Rivas et al. 2016].

Hinsichtlich RRT war die Reduktion der Inzidenzrate in der Bevölkerung mit Diabetes bei der Auswertung mit Krankenkassendaten in guter Übereinstimmung mit dem bereits in den 2000er und 2010er Jahren in USA und Spanien beobachteten Rückgang [Burrows et al. 2014, Burrows et al. 2017, Comas et al. 2012, Lorenzo et al. 2010]. Allerdings ist die Vergleichbarkeit nur eingeschränkt gegeben, da im Gegensatz zu der hier präsentierten Forschungsarbeit bei Menschen mit Diabetes nur RRT-Ereignisse aufgrund einer diabetischen Nephropathie gezählt wurden, die lediglich rund die Hälfte aller RRT in dieser Population ausmachen.

Die Inzidenzrate von Amputationen in der Bevölkerung mit Diabetes ging in beiden Forschungsarbeiten wie in der früheren nationalen Studie aus Leverkusen [Trautner et al. 2007] zurück, wobei der Rückgang deutlicher und nun auch in der Bevölkerung ohne Diabetes erkennbar war. In diesem Kontext erscheint jedoch erwähnenswert, dass die einzige, relativ gut vergleichbare Studie aus Italien keine Veränderung der Inzidenz von Amputationen, weder bei Menschen mit noch ohne Diabetes, fand [Giorda et al. 2018]. Studien aus Spanien und Schweden hatten sogar über einen Anstieg der Amputationsinzidenz in der Bevölkerung mit Diabetes berichtet [Almaraz et al. 2012, Buckley et al. 2012]. Die Vergleichbarkeit war jedoch stark eingeschränkt, da in diesen Studien jede Hospitalisierung als Ereignis gezählt wurde.

Der in beiden Forschungsarbeiten beobachtete deutliche Rückgang der Major-Amputationsinzidenz sowohl bei Menschen mit als auch ohne Diabetes war gut vergleichbar mit den Ergebnissen der früheren nationalen Studie aus Leverkusen sowie der Studien aus Italien, Finnland und Japan [Trautner et al. 2007, Lombardo et al. 2014, Ikonen et al. 2010, Kamitani et al. 2021]. Dagegen konnte der ebenfalls in beiden präsentierten Originalarbeiten beobachtete deutliche Rückgang der Minor-Amputationsinzidenz bei Menschen mit Diabetes in Italien und Japan nicht festgestellt werden [Lombardo et al. 2014, Kamitani et al. 2021].

Bei Herzinfarkten kann ein Rückgang der Inzidenzrate bei Männern mit Diabetes in Deutschland in der 2010er Dekade erstmals beobachtet werden, während diese Zahl noch in den 1990er und 2000er Jahren angestiegen war [Icks et al. 2010]. Die Zeittrends waren hier wie bereits in der Studie aus Schweden geschlechterspezifisch [Rautio et al. 2008].

Beim Vergleich des relativen Risikos zwischen Menschen mit und ohne Diabetes mit früheren nationalen sowie internationalen Forschungsarbeiten fällt auf, dass die relativen Unterschiede in den hier vorgestellten Arbeiten überwiegend deutlich niedriger sind. So war bzgl. Erblindung das relative Risiko in der früheren Arbeit aus Deutschland bei Faktor fünf [Icks et al.], während es in der hier vorgestellten Arbeit durchweg unter zwei lag. Studien aus Spanien und Schweden beispielsweise beobachteten relative Risiken in der Größenordnung drei bis acht für einen Schlaganfall, wohingegen diese Zahl in der hier präsentierten Arbeit unter zwei lag. Bei RRT haben die beiden methodisch vergleichbarsten Studien aus Kanada und Italien relative Risiken in der Größenordnung zwischen 8 und 12 gesehen [Lok et al. 2004, Giorda et al. 2018], während diese Zahl in beiden hier präsentierten Forschungsarbeiten nur zwischen vier und sechs lag. Ebenso stellte sich der Wert für das relative Risiko bei Amputationen in den beiden hier vorgestellten Forschungsarbeiten mit Größenordnung acht bis neun etwas niedriger dar im Vergleich zu den methodisch relativ vergleichbaren internationalen Arbeiten aus Schottland, Frankreich und Italien. Dort lag diese Zahl geschätzt zwischen 10 und 12 [Morris et al. 1998, Fosse et al. 2009, Lombardo et al. 2014]. Einzig war das relative Risiko in den hier vorgestellten Arbeiten etwas höher als das auf 7,4 geschätzte in der früheren nationalen Studie basierend auf Krankenkassendaten [Icks et al. 2009]. Das relative Risiko

bzgl. Major als auch Minor-Amputation war in beiden Forschungsarbeiten ebenfalls etwas niedriger als in den relativ gut vergleichbaren Studien aus Italien, Japan und Finnland [Lombardo et al. 2014, Kamitani et al. 2021, Ikonen et al. 2010]. Einzig bei Herzinfarkt ist das relative Risiko in der hier vorgestellten sich im Einreichungsprozess befindenden Forschungsarbeit mit Größenordnung zwei bis vier vergleichbar hoch wie in den methodisch am besten vergleichbaren internationalen Studien aus Schottland, Finnland, Schweden und USA [Read et al. 2019, Barengo et al. 2008, Rautio et al. 2005, Carson et al. 2014].

Es stellt sich die Frage, worauf der erkannte Rückgang der Inzidenzrate der hier untersuchten Endstadien der mit Diabetes assoziierten Komplikationen in der Bevölkerung mit Diabetes zurück zu führen ist. Hierfür liegen zwei grundlegend verschiedene Erklärungsansätze nahe. Zum einem könnte es daran liegen, dass sich die Versorgung von Menschen mit Diabetes in den 2000er und 2010er Jahren grundlegend verbessert hat. So könnte insbesondere die Einführung neuer antihyperglykämischer Medikamente in den 2010er Jahren (z.B. SGLT2 Inhibitoren, GLP1 Rezeptor Agonisten) einen Beitrag für den Rückgang der Inzidenzrate geleistet haben. Der Rückgang der Erblindung in der Bevölkerung ohne Diabetes könnte zudem erklärt werden mit der Einführung effektiver Therapien (Anti-VEGF) hinsichtlich der altersabhängigen Makuladegeneration in den 2000er Jahren [Schorr et al. 2016]. Weiterhin könnte die Einführung der Disease Management Programme (DMP) zum Typ-1- und Typ-2-Diabetes in 2002 zwecks früherer Erkennung von diabetischen Komplikationen eine maßgebliche Rolle für die Reduktion gespielt haben. Der zweite Erklärungsansatz beruht auf einer im Zeitraum der Studien erfolgten besseren sowie früheren Erkennung eines vorher unentdeckten Diabetes durch verbesserte Screening Methoden. Es ist davon auszugehen, dass Menschen mit einem unentdeckten Diabetes einen leichteren Erkrankungsverlauf haben. So führt eine frühere Erkennung des Diabetes dazu, dass die Population der Menschen mit Diabetes insgesamt ‚gesünder' (im Sinne von weniger stark erkrankt) ist und deshalb seltener eine der mit Diabetes assoziierten Komplikationen erleidet. Die Reduktion des relativen Risikos bei den meisten mit Diabetes assoziierten Komplikationen spricht folglich dafür, dass

sich die Inzidenzrate in der diabetischen Population mehr reduziert hat als in der nichtdiabetischen Population.

Insgesamt lässt sich sagen: Die Inzidenzraten für die mit Diabetes assoziierten Komplikationen haben sich insbesondere für Menschen mit Diabetes in den letzten Dekaden erfreulicherweise deutlich reduziert. Allerdings sind sie noch immer erkennbar höher als in der nichtdiabetischen Population. Es besteht daher nach wie vor Handlungsbedarf bzgl. Vorsorge und Therapie bei Menschen mit Diabetes sowie die Notwendigkeit für weitere Forschung.

5.3 Limitationen und Ausblick

Die hier einbezogenen Forschungsarbeiten weisen trotz vieler methodischer Verbesserungen weiterhin Limitationen auf. So war es nicht möglich, eine nahezu vollständige deutschlandweite Population für die Untersuchung der Inzidenzraten zu rekrutieren. Insbesondere die Registerstudien zu Erblindung, Schlaganfall, RRT und Herzinfarkt waren immer noch nur auf einzelne Regionen, teilweise sogar nur einzelne Städte bzw. Landkreise beschränkt und daher eingeschränkt aussagekräftig für ganz Deutschland. Ebenso beschränkten sich die Forschungsarbeiten mit deutschen Krankenkassendaten auf gesetzlich Versicherte einzelner Krankenkassen. Hier war zudem der Beobachtungszeitraum auf fünf bis sieben Jahre beschränkt, sodass noch keine Langzeittrends erfasst werden konnten. Eine weitere Limitation der Studien mit Sozialamt-, Register- und Dialysepraxisdaten (mit Ausnahme des Herzinfarktregisters Augsburg) war, dass die Schätzung der Bevölkerung mit Diabetes nach wie vor auf deutschlandweiten Surveys basierte da repräsentativere regionale Diabetesprävalenzschätzungen bislang fehlen. Ebenso musste die Diabetesprävalenz zwischen den Jahren, wo Surveys stattfanden, linear interpoliert und teilweise sogar extrapoliert werden, so dass Schwankungen der Diabetesprävalenz nicht immer adäquat abgebildet werden konnten.

Eine besondere Problematik bietet zudem der unbekannte (nicht diagnostizierte) Diabetes. Es ist davon auszugehen, dass bis zur Hälfte aller Personen mit Typ 2 Diabetes nicht wissen, dass sie bereits erkrankt sind [Tamayo et al. 2014]. In den Originalarbeiten, in denen Krankenkassen- und Sozialamtdaten sowie die Daten des KORA-Registers ausgewertet wurden, war die Erfassung des unbekannten Diabetes nicht möglich. Von daher lässt sich eine Missklassifikation des Diabetesstatus in den dort verwendeten Datenquellen nicht ausschließen, mit der Folge, dass die wahre Diabetesprävalenz unterschätzt wird. Dagegen war es in den Forschungsarbeiten zur Schlaganfallinzidenz und der RRT-Inzidenz im Kreis Mettmann möglich, bei allen Personen mit inzidenter Erkrankung den unbekannten Diabetes zu erfassen aufgrund durchgeführter HbA1c-Messungen. Grundlage für die Schätzung der Diabetesprävalenz waren hier die Bundesgesundheitsbefragungen BGS98 (1997-1999) und DEGS (2008-2011), bei denen jeweils ebenfalls HbA1c-Messungen stattfanden [RKI 2000, RKI 2013, RKI 2014, RKI 2015].

Bei dem Verwenden von Krankenkassendaten besteht ferner die Limitation, dass es nicht immer möglich war, das erste jemals stattgefundene Ereignis zu erfassen. Dies hat zur Folge, dass Vergleiche mit Registerdatenstudien nur eingeschränkt möglich sind. Eine generelle Limitation, die alle bisher durchgeführten Forschungsarbeiten gemeinsam haben, ist die fehlende Berücksichtigung weiterer klinischer Einflussfaktoren bzw. potentieller Confounder wie Lebensstil, klinische Marker oder andere Komorbiditäten, bei denen von einem Zusammenhang zwischen Diabetes und Erkrankung auszugehen ist.

Die vorliegenden Forschungsarbeiten konnten nicht den Einfluss der COVID-19 Pandemie ab März 2020 auf die zeitliche Entwicklung der mit Diabetes assoziierten Komplikationen untersuchen, da die Datenerhebungen der erhobenen Forschungsdaten vor Beginn der Pandemie erfolgten. Eine in unserer Arbeitsgruppe durchgeführte Auswertung der Hospitalisierungsraten der Jahre 2017 bis 2020 bei Menschen mit und ohne Diabetes basierend auf Krankenkassendaten der AOK Rheinland/Hamburg zielte auf die Frage ab, inwiefern der zeitliche Trend im ersten Pandemiejahr von den Jahren zuvor abwich [Claessen et al. 2022]. Bemerkenswert war, dass bei Menschen mit Diabetes die Hospitalisierungsrate

wegen Major-Amputation in 2020 deutlich angestiegen ist, was einem genau entgegengesetzten Trend der hier vorgestellten Forschungsarbeiten entspricht. Gleichzeitig sank die Hospitalisierungsrate wegen eines Diabetischen Fußsyndroms. Dasselbe gilt für den Herzinfarkt bezogen auf 2020. Bei Schlaganfällen hingegen verblieb diese Zahl auf dem Niveau der Vorjahre. Mögliche Gründe für den Anstieg der Majoramputationen bei einem gleichzeitigen Rückgang der Hospitalisierung bei diabetischem Fusssyndrom sind reduzierte oder verspätete Behandlungen durch verminderte Leistungsangebote in Krankenhäusern sowie eine verminderte Inanspruchnahme durch Menschen mit Diabetes aufgrund der Angst vor COVID-19 während der Lockdowns. Eine Fortführung der Untersuchung des zeitlichen Trends der mit Diabetes assoziierten Komplikationen bei Menschen mit und ohne Diabetes über das Jahr 2020 hinaus erscheint daher ausgesprochen sinnvoll. Die vorliegend aufgezeigte Datenlage weist deutlich darauf hin, dass eine erfolgreiche Umsetzung des St.Vincent Ziels in der Bevölkerung mit Diabetes mit Ausnahme von Erblindungen selbst 30 Jahre nach der Deklaration noch nicht, bzw. nur bedingt erreicht wurde. Auch von daher liegt weiterer epidemiologischer Forschungsbedarf auf der Hand. Naheliegendes Ziel sollte es sein, die Datenlage dahingehend weiter auszubauen, dass möglichst bundesweite Kollektive über längere zeitliche Trends untersucht werden können. Dies erscheint aus epidemiologischer Sicht überfällig. Neben der Untersuchung der Amputationen und RRT könnten auch Schlaganfälle auf der Basis von Krankenkassendaten untersucht werden. Die Analyse von Erblindungsinzidenzen basierend auf Blindengeldempfängerdaten könnte ausgedehnt werden, was bisher nur in Sachsen erfolgte [Claessen et al. 2021]. Für die Analyse von Herzinfarktinzidenzen sollten weiterhin Registerdaten zur Anwendung kommen, da aufgrund der immer noch hohen Letalität des Herzinfarkts diese Ereignisse nur unvollständig mit Krankenkassendaten abgebildet werden können. Neben alters- und geschlechtsadjustierten Schätzungen der Inzidenzraten bietet sich an den zeitlichen Trend in zukünftigen Arbeiten auch nach Alter und Geschlecht stratifiziert zu untersuchen. Eine der vorliegenden Forschungsarbeiten konnte bereits aufzeigen, dass zeitliche Entwicklungen nach Altersgruppe und Geschlecht variieren können. Die diesbezügliche Notwendigkeit wird unterstrichen durch

Studienergebnisse aus den USA, wo in den frühen 2010er Jahren ein Anstieg der Inzidenz von RRT, Schlaganfall, Amputation und Herzinfarkt nur bei 18-45-jährigen gesehen wurde [Gregg et al. 2019].

5.4 Fazit

Insgesamt stellen die Originalarbeiten dieser Schrift für die Forschung zum zeitlichen Trend vom Auftreten von mit Diabetes assoziierten Komplikationen in der Bevölkerung mit und ohne Diabetes einen substantiellen Fortschritt dar**.** Sie zeigen vor allem die Notwendigkeit populationsbasierter Studien mit längerem Beobachtungszeitraum und einer validen Schätzung der Bevölkerung mit Diabetes auf. Ebenso belegen sie die Notwendigkeit für eine vollständige und kontinuierliche Erfassung der mit Diabetes assoziierten Komplikationen sowie der Anwendung von Alters- und Geschlecht- adjustierten und stratifizierten Schätzungen angesichts einer möglicherweise steigenden Inzidenz in jüngeren Altersgruppen. Abschließend ist festzustellen, dass noch umfassendere und verstärkt repräsentative Studienpopulationen benötig werden. Obwohl weitere Forschung unerlässlich erscheint, zeigen die Arbeiten eine deutliche Verbesserung der Situation von Menschen mit Diabetes, allerdings noch immer Verbesserungspotential. Die weitere Untersuchung, inwieweit die Ziele der St. Vincent Deklaration realisiert werden, scheint auch aktuell von evidenter Bedeutung.

6. Literaturverzeichnis

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8 Anhang Originalarbeiten

Der Anhang der eigenen Originalarbeiten erfolgt mit freundlicher Genehmigung der Verlage

1. **Claessen H**, Kvitkina T, Narres M, Trautner C, Zöllner I, Icks A (2018): Decreasing incidence of blindness in people with and without diabetes in southern Germany, 2008–2012. ***Diabetes Care*** 41(3):478-484.

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Markedly Decreasing Incidence of Blindness in People With and Without Diabetes in Southern Germany

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EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

OBJECTIVE

Studies comparing the incidence of blindness in persons with and without diabetes are scarce worldwide. In Germany, a decline in the incidence of blindness was found during the 1990s. The aim of this study was to analyze the recent time trend.

RESEARCH DESIGN AND METHODS

Data were based on administrative files in southern Germany to assess recipients of blindness allowance newly registered between 1 January 2008 and 31 December 2012. We estimated age- and sex-standardized incidence of blindness in people with and people without diabetes and the corresponding relative risk. Poisson regression was used to examine age- and sex-adjusted time trends.

RESULTS

We identified 1,897 new cases of blindness (23.7% of which were associated with diabetes). We observed a strong decrease in incidence in both the population with diabetes (2008, 17.3 per 100,000 person-years [95% CI 13.6–21.1], and 2012, 8.9 per 100,000 person-years [6.3–11.6]: 16% decrease [10–22] per year) and that without diabetes (2008, 9.3 per 100,000 person-years [8.3–10.3], and 2012, 6.6 [5.8–7.4]: 9% decrease [5–13] per year). The relative risk comparing those incidences was 1.70 (95% CI 1.32–2.16) and remained constant in the observation period. Regarding time trend, we found similar results for both sexes.

CONCLUSIONS

We found a significant reduction in incidence of blindness in the populations with and without diabetes, which was more prominent among individuals with diabetes compared with the 1990s. Our findings may be explained by effective secondary prevention therapies and improved ophthalmologic care beyond diabetic retinopathy, particularly regarding macular degeneration, which means earlier detection and earlier and better treatment.

Diabetes is a highly prevalent chronic disease with the global prevalence of 8.8% among adults (20–79 years of age) in 2015 corresponding to 415 million people (1). Furthermore, diabetes can cause both macrovascular complications (stroke and peripheral and coronary artery disease) and microvascular complications such as diabetic nephropathy, neuropathy and retinopathy, which may lead to blindness. Thus, diabetes has been shown to be one of the leading causes of blindness in Western countries in the working-age population (2–5).

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The St. Vincent Declaration in Europe (1989) aimed to improve diabetes treatment and thus reduce the risk of diabetes-related blindness by one-third in 5 years (6). For analysis of any improvements, the collection of data on diabetes-related blindness was initiated at the beginning of the 1990s. Furthermore, the national German guidelines "Prevention and Therapy of Retinal Complications in Diabetes" aimed at an earlier detection of diabetic retinopathy, appropriate treatment, and the reduction of the incidence of blindness (7). However, surveillance for blindness among persons with diabetes has not been conducted nationally, and population-based data on incidence of blindness in the population with compared with the population without diabetes are scarce worldwide.

In our previous study covering the period 1990–1993 in two districts in Germany (parts of Baden-Württemberg and North Rhine-Westphalia), the incidence of blindness was found to be ~60.6 per 100,000 person-years in people with diabetes and 11.6 in the population without diabetes, resulting in a relative risk (RR) of 5.2 (8). In a subsequent study conducted in the same study area using data from 1990 to 1998, it was shown that the incidence of blindness decreased by 3% per year in the population with diabetes but remained constant among individuals without diabetes (6). Incidence of blindness was ascertained again in a study in 2008 covering neighboring parts of Baden-Württemberg showing that the RR of blindness between individuals with and individuals without diabetes decreased to the factor 2.4 (5). Approximately 59% of the risk of becoming blind in people with diabetes, and 9% of this risk in the entire population, was attributable to diabetes. The incidences were significantly lower compared with the earlier study in both the population with and the population without diabetes (8,9). The reduction of incidence in this study was more pronounced in the population with diabetes, where a significant decline had already been found during the period between 1990 and 1998 (9). However, the investigation of time trend was limited, since the regions were not exactly the same and we did not collect data between 1999 and 2007.

A significant decline in blindness incidence due to diabetes over approximately the same time span was also observed in Poland and Scotland (10,11). However, these studies did not adjust for age and sex, and no comparison with the population without diabetes was made. To the best of our knowledge, no studies have analyzed incidence of blindness in the population with or the population without diabetes except studies from Germany (3,5,9).

The aim of this study was to estimate the time trend of incidence rate (IR) of blindness in people with and people without diabetes in Germany and the corresponding relative and attributable risk over a 5-year period in a more recent timeframe. The study is part of a recent evaluation of late complications of diabetes according to the goals of the St. Vincent Declaration (6).

RESEARCH DESIGN AND METHODS

Database and Identification of Patients

We used the administrative files of the welfare administration (35 rural and 10 urban districts in the federal state of Baden-Württemberg, southern Germany) to assess all individuals who were newly registered as blindness allowance recipients between 1 January 2008 and 31 December 2012.

For our analysis, we included data from 22 of these 45 districts where a written medical statement was available that documented all relevant diseases, including diabetes. Of these 22 districts, we had to exclude 1 owing to incomplete data. In total, 1,903 new blindness allowance recipients were registered, of whom 6 had to be excluded owing to missing diabetes status.

Outcomes

A detailed description of the database and the blindness allowance procedure has previously been published (5). Briefly, all recipients of the blindness allowance were included who fulfilled the German criteria for blindness (visual acuity of 0.02 or less, based on the best corrected acuity in the better eye; visual field reduced to a radius of 5° or less or equivalent reduction of vision caused by, for example, central scotoma, making the person unable to find his or her way; or morphological correlates that explain the blindness) regardless of their income. Applying this approach, which was used in earlier studies (3–5,9), we therefore could expect an almost complete collection rate of newly blind subjects.

Population data were obtained by the Federal Office of Statistics (12). The total population in the study region as of 31 December 2010 was 4,823,570, which corresponds to approximately half of the entire population of Baden-Württemberg. The population with diabetes was estimated by applying the age- and sex-specific diabetes prevalence of the German Health Update (GEDA) surveys of 2009, 2010, and 2012 (13–15). With regard to the year 2008, we assumed that the diabetes prevalence was the same as in the year 2009, since the GEDA survey of 2009 had already started in July 2008. Regarding the year 2011, we used the arithmetic mean of the estimates in 2010 and 2012.

Statistical Analysis

We performed the main analyses for the entire population as well as separately for men and women. We estimated the population with diabetes in each stratum, defined by sex and age (≤30, 30–39, 40–49, 50–59, 60–69, 70–79, 80–89, and ≥90 years) by multiplying the study population with the estimated age- and sex-specific prevalence of diabetes. We calculated stratum-specific and directly standardized IRs of blindness with 95% CIs in the estimated population with and population without diabetes for each calendar year using the German population of 2010 as the standard population. Furthermore, we estimated IR ratio (IRR) as well as attributable risk of blindness comparing the population with versus without diabetes from the standardized IRs.

In order to examine time trends, we first fitted Poisson regression models with IR of blindness as the dependent variable and year of blindness as linear continuous difference from baseline year 2008 as the independent variable. These models were calculated separately for individuals with and without diabetes and were adjusted for age. The three lowest age classes (i.e., ≤30, 30–39, and 40–49 years) were combined into one group (≤50 years) because of convergence problems of some models and were therefore used as a reference group. Furthermore, we performed analogous Poisson models for the entire population. In these models, we additionally included a variable presence of diabetes ("yes" vs. "no") as well as an interaction term for diabetes and years since 2008.

All analyses were conducted with the descale adjustment to take into account overdispersion of the outcome variable, which was based on cumulated data

on the covariate strata year * sex * age class * diabetes. We performed analysis using the statistical analysis system SAS (SAS for Windows 7, release 9.4 TS1M1; SAS Institute, Cary, NC).

Ethics

The study was performed in accordance with the Declaration of Helsinki for research involving human subjects and the good epidemiological practice guideline (16).

RESULTS

Study Population

In our study region, we identified 1,897 new registered blindness allowance recipients in the years 2008–2012. The age- and sex-frequency distributions are shown in Table 1. Most of those with new cases of blindness were female (62.5%) and were >80 years of age (54.8%). Among persons without diabetes, ~8% were <30 years of age and 14% older than 90 years of age. In contrast, none were younger than 30 years of age among individuals with diabetes and solely 7% were >90 years of age (Supplementary Data). The age distribution remained nearly constant during the years 2008–2012, which was true in both groups: persons with and persons without diabetes (Supplementary Data). Almost one-quarter of those with new cases of registered blindness allowances were classified as having diabetes, with similar proportions in both sexes, which substantially decreased from 26.1% in 2008 to 20.7% in 2012. In contrast, the diabetes prevalence in the background population changed only marginally in the same time interval (2008, 7.1%, and 2012, 7.3%).

Incidence Rate and RR

The age- and sex-standardized IRs of blindness are presented in Table 2. We observed a strong decrease of IR per 100,000 person-years in the population with diabetes (2008, 17.3 [95% CI 13.6–21.1], and 2012, 8.9 [6.3–11.6]), with a particularly strong decrease in the first 3 years. Likewise, we found a somewhat weaker but still considerable decrease of IR in the population without diabetes (2008, 9.3 [8.3–10.3], and 2012, 6.6 [5.8–7.4]). In general, these results did not alter between sexes, with the exception that the decrease in the population with diabetes was somewhat stronger among women. The IRR comparing the incidence of blindness between persons with and persons without diabetes ranged between 1.3 (95% CI 1.0–1.7) in 2010 and 1.9 (1.5–2.4) in 2008. The attributable risk of blindness among the population with diabetes ranged between 0.24 (95% CI 0.01–0.42) and 0.46 (0.32–0.58), while the attributable risk of blindness in the total population lay between 0.03 (95% CI 0.00–0.12) and 0.10 (0.08–0.12).

Analysis of Time Trend and Other Covariates

The results of the incidence trend from the fully adjusted Poisson models are presented in Table 3. The RRs in the population stratified for diabetes status are shown in models 1a and 1b. We observed a significant decline in the blindness incidence in the population with diabetes during the observation period by 16% per year (RR per calendar year 0.84 [95% CI 0.78–0.90]). This decrease was seen in both sexes, with a somewhat stronger decline among women. The IR was ~20% lower among men compared with women (RR 0.80 [0.66–0.99]). The IR strongly increased with age among women but not among men.

When considering the population without diabetes, we observed a weaker albeit significant decrease in blindness incidence by 9% per year (RR 0.91 [95% CI 0.87–0.95]). No difference was seen between men and women, while this IR increases strongly with age.

When considering the entire population in model 2, we found a 70% increased IR in the population with diabetes compared with the population without diabetes (RR 1.70 [95% CI 1.32–2.16]) with comparable results in both sexes.

This difference was particularly strong among the younger age-groups and was even reversed in the oldest age-group (RR diabetes vs. no diabetes, age <50 years, 3.11 [95% CI 1.56–6.18]; 90+ years, 0.57 [0.36–0.88]) (data not shown). The interaction diabetes * calendar year was nonsignificant, indicating that the RR comparing the population with and without diabetes did not materially alter, which was true for both sexes.

CONCLUSIONS

Main Findings

We estimated IRs, RRs, and attributable risk of blindness comparing people with and without diabetes and their time trend in a large region in southern Germany between 2008 and 2012. We found a significant reduction in incidence of blindness in both the population with and that without diabetes, which was in particular strong between 2008 and 2010, with a somewhat stronger decline among individuals with diabetes. However, the risk of blindness remained significantly increased among individuals with diabetes compared with people without diabetes, with RR ranging between 1.3 and 1.9. We observed similar results in both sexes with regard to time trend.

Comparison With Other Studies and Implications

Compared with the 1990s, the regional IR of blindness in Germany markedly declined (17) (Fig. 1). This decrease was observed in both populations with diabetes (1990, 48.4 per 100,000 person-years [95% CI 35.3–61.4], and 2012, 17.3 per 100,000 person-years [13.6–21.1]) and without diabetes (1990, 12.2 per 100,000 person-years [11.1–13.4], and 2012, 6.6 per 100,000 person-years [5.8–7.4]), with a much more prominent decline in the population with diabetes, leading to a markedly reduced RR from 4.0 in 1990 to 1.4 in 2012 (5,9). Unfortunately, the study region of the analysis in the 1990s is not exactly the same as that in our study, but they are neighboring districts with a similar age distribution. The observed reduction at first seems surprising owing to the aging of the population. However, this decrease remained after age standardization. The substantial decrease in blindness due to diabetic retinopathy was already shown in Germany, which could be explained by several factors (e.g., improved treatment of diabetes, better collaboration between diabetologists and ophthalmologists, better ophthalmologic diagnostics and therapy for diabetic macula edema via optical coherence tomography, as well as intravitreal medication with vascular endothelial growth factor [VEGF] inhibitors or steroids) (18).

A possible explanation for the decrease in incidence in the population without but also with diabetes could be improved early detection and treatment of macular degeneration, the treatment of glaucoma, and markedly increased cataract surgery (19). A substantial reduction in blindness due to age-related macular degeneration, which is the main cause of blindness, in the previous two decades was observed in southern Germany (3). This finding was also confirmed by a

Table 1—Description of all persons with first blindness and the background population, Baden-Württemberg, 2008–2012

						Men		Women	
	Total	Men	Women	Diabetes	No diabetes	Diabetes*	No diabetes*	Diabetes*	No diabetes*
All years combined									
Persons with blindness†	1,897	712 (37.5)	1,185 (62.5)	449 (23.7)	1,448 (76.3)	167 (23.5)	545 (76.5)	282 (23.8)	903 (76.2)
Total person-years	24,027,101	11,780,875 (49.0)	12,246,226 (51.0)	1,748,049 (7.3)	22,279,052 (92.7)	827,861 (7.0)	10,953,014 (93.0)	11,326,038 (92.5)	920,188 (7.5)
Age at time of first blindness (years)									
≤30	121	61 (50.4)	60 (49.6)	0 (0.0)	121 (100.0)	0 (0.0)	61 (100.0)	0 (0.0)	60 (100.0)
30–39	40	24 (60.0)	16 (40.0)	3 (7.5)	37 (92.5)	3 (12.5)	21 (87.5)	0 (0.0)	16 (100.0)
40–49	64	35 (54.7)	29 (45.3)	11 (17.2)	53 (82.8)	9 (25.7)	26 (74.3)	2 (6.9)	27 (93.1)
50–59	115	56 (48.7)	59 (51.3)	41 (35.7)	74 (64.3)	22 (39.3)	34 (60.7)	19 (32.2)	40 (67.8)
60–69	149	74 (49.7)	75 (50.3)	54 (36.2)	95 (63.8)	26 (35.1)	48 (64.9)	28 (37.3)	47 (62.7)
70–79	369	162 (43.9)	207 (56.1)	107 (29.0)	262 (71.0)	44 (27.2)	118 (72.8)	63 (30.4)	144 (69.6)
80–89	807	247 (30.6)	560 (69.4)	202 (25.0)	605 (75.0)	60 (24.3)	187 (75.7)	142 (25.4)	418 (74.6)
≥90	232	53 (22.8)	179 (77.2)	31 (13.4)	201 (86.6)	3 (5.7)	50 (94.3)	28 (15.6)	151 (84.4)
Year of first blindness: 2008									
Persons with blindness†	467	174 (37.3)	293 (62.7)	122 (26.1)	345 (73.9)	46 (26.4)	128 (73.6)	76 (25.8)	217 (74.1)
Total population	4,816,006	2,358,576 (49.0)	2,457,430 (51.0)	344,252 (7.1)	4,471,754 (92.9)	158,955 (6.7)	2,199,621 (93.3)	185,297 (7.5)	2,272,133 (92.5)
Year of first blindness: 2009									
Persons with blindness†	404	140 (34.7)	264 (65.3)	104 (25.7)	300 (74.3)	29 (20.7)	111 (79.3)	75 (28.4)	189 (71.6)
Total population	4,816,733	2,360,698 (49.0)	2,456,035 (51.0)	349,195 (7.2)	4,467,538 (92.8)	162,004 (6.9)	2,198,694 (93.1)	187,191 (7.6)	2,268,844 (92.4)
Year of first blindness: 2010									
Persons with blindness†	388	143 (36.9)	245 (63.1)	84 (21.6)	304 (78.4)	31 (21.7)	112 (78.3)	53 (21.6)	192 (78.4)
Total population	4,823,570	2,367,327 (49.1)	2,456,243 (50.9)	352,908 (7.3)	4,470,662 (92.7)	170,451 (7.2)	2,196,876 (92.8)	182,457 (7.4)	2,273,786 (92.6)
Year of first blindness: 2011									
Persons with blindness†	314	130 (41.4)	184 (58.6)	72 (22.9)	242 (77.1)	32 (24.6)	98 (75.4)	40 (21.7)	144 (78.3)
Total population	4,838,304	2,378,244 (49.2)	2,460,060 (50.8)	355,568 (7.3)	4,482,736 (92.7)	171,466 (7.2)	2,206,778 (92.8)	184,102 (7.5)	2,275,958 (92.5)
Year of first blindness: 2012									
Persons with blindness†	324	125 (38.6)	199 (61.4)	67 (20.7)	257 (79.3)	29 (23.2)	96 (76.8)	38 (19.1)	161 (80.9)
Total population	4,732,488	2,316,030 (48.9)	2,416,458 (51.1)	346,126 (7.3)	4,386,362 (92.7)	164,985 (7.1)	2,151,045 (92.9)	181,141 (7.5)	2,235,317 (92.5)

Data are *n* or *n* (%). *Percentages related to total male population and female population, respectively. †Related to total population.

Table 2—Incidence of blindness, Germany, 2008–2012

	IR (95% CI) per 100,000 person-years*			IRRs and attributable risk (95% CI)		
	IRt	IRd	IRn	IRR	ARE	PAR
Total population						
2008	10.3 (9.4–11.3)	17.3 (13.6–21.1)	9.3 (8.3–10.3)	1.9 (1.5–2.4)	0.46 (0.32–0.58)	0.10 (0.08–0.12)
2009	8.7 (7.9–9.6)	14.3 (10.8–17.9)	7.8 (6.9–8.7)	1.8 (1.4–2.4)	0.45 (0.28–0.58)	0.10 (0.00–0.21)
2010	8.1 (7.3–9.0)	10.4 (7.8–13.0)	7.9 (7.0–8.8)	1.3 (1.0–1.7)	0.24 (0.01–0.42)	0.03 (0.00–0.12)
2011	6.4 (5.7–7.1)	10.8 (6.6–15.0)	6.0 (5.2–6.7)	1.8 (1.2–2.7)	0.45 (0.17–0.63)	0.06 (0.00–0.21)
2012	6.8 (6.1–7.6)	8.9 (6.3–11.6)	6.6 (5.8–7.4)	1.4 (1.0–1.9)	0.26 (0.00–0.46)	0.03 (0.00–0.16)
Male population						
2008	9.6 (8.1–11.0)	16.6 (10.6–22.5)	8.6 (7.0–10.1)	1.9 (1.3–2.9)	0.48 (0.23–0.65)	0.11 (0.08–0.14)
2009	7.3 (6.1–8.5)	11.7 (6.0–17.4)	7.0 (5.6–8.3)	1.7 (1.0–2.8)	0.41 (0.00–0.65)	0.05 (0.00–0.25)
2010	7.5 (6.2–8.7)	9.1 (5.6–12.7)	7.5 (6.1–9.0)	1.2 (0.8–1.9)	0.17 (0.00–0.47)	0.00 (0.00–0.16)
2011	6.6 (5.5–7.8)	13.3 (5.5–21.1)	6.2 (5.0–7.5)	2.1 (1.1–4.0)	0.53 (0.13–0.75)	0.06 (0.00–0.28)
2012	6.7 (5.5–7.9)	9.6 (5.3–14.0)	6.5 (5.1–7.8)	1.5 (0.9–2.5)	0.33 (0.00–0.59)	0.03 (0.00–0.24)
Female population						
2008	10.7 (9.5–11.9)	17.7 (12.9–22.5)	9.6 (8.3–10.9)	1.8 (1.4–2.5)	0.46 (0.26–0.60)	0.10 (0.08–0.13)
2009	9.4 (8.3–10.6)	15.5 (11.5–19.4)	8.2 (7.0–9.4)	1.9 (1.4–2.5)	0.47 (0.29–0.61)	0.13 (0.00–0.25)
2010	8.4 (7.4–9.5)	10.7 (7.1–14.3)	8.1 (6.9–9.2)	1.3 (0.9–1.9)	0.25 (0.00–0.48)	0.04 (0.00–0.15)
2011	6.3 (5.4–7.2)	8.2 (5.3–11.1)	5.9 (4.9–6.9)	1.4 (0.9–2.1)	0.28 (0.00–0.52)	0.06 (0.00–0.25)
2012	6.8 (5.9–7.8)	7.7 (4.9–10.5)	6.7 (5.7–7.8)	1.1 (0.8–1.7)	0.13 (0.00–0.42)	0.02 (0.00–0.19)

ARE, attributable risk of blindness in the population with diabetes; IRd, IR of blindness in individuals with diabetes in population with diabetes; IRn, IR of blindness in individuals without diabetes in population without diabetes; IRt, IR of blindness in total population; PAR, attributable risk of blindness in the total population. *Standardized to the German population, 2010.

Danish study indicating a decrease between 2000 and 2010, with a particularly strong decrease after 2006, when the intravitreal pharmacotherapy with inhibitors of VEGF therapy was introduced (20). The first indication of intravitreal anti-VEGF therapy in 2006 was the age-related macular degeneration. The indications of its use were extended to many pathologies,

Table 3—Results of Poisson models: RR for blindness, Germany 2008–2012

	RR (95% CI) for blindness‡		
Variables	Total population	Men	Women
Model 1a (population with diabetes)			
Calendar year	0.84 (0.78–0.90)*	0.88 (0.79–0.98)*	0.82 (0.77–0.87)*
Male vs. female	0.80 (0.66–0.99)*	—	—
Age (years)†			
≥90	17.52 (9.04–33.95)*	2.96 (0.84–10.49)	93.53 (31.02–281.99)*
80–89	19.58 (11.10–34.54)*	7.59 (4.08–14.11)*	90.45 (30.91–264.64)*
70–79	4.99 (2.78–8.94)*	2.01 (1.06–3.81)*	22.76 (7.71–67.22)*
60–69	3.22 (1.74–5.97)*	1.39 (0.70–2.76)	13.88 (4.60–41.85)*
50–59	3.09 (1.63–5.84)*	1.25 (0.62–2.53)*	14.12 (4.60–43.30)*
Model 1b (population without diabetes)			
Calendar year	0.91 (0.87–0.95)*	0.92 (0.86–0.98)*	0.91 (0.85–0.96)*
Male vs. female	0.94 (0.83–1.06)	—	—
Age (years)†			
≥90	94.60 (75.87–117.95)*	92.86 (64.29–134.12)*	97.76 (71.32–134.01)*
80–89	48.82 (40.84–58.35)*	44.15 (34.05–57.25)*	52.23 (39.82–68.52)*
70–79	10.10 (8.23–12.4)*	10.06 (7.56–13.40)*	10.21 (7.43–14.04)*
60–69	2.99 (2.27–3.93)*	3.11 (2.14–4.52)*	2.88 (1.87–4.45)*
50–59	1.64 (1.21–2.21)*	1.52 (1.00–2.33)*	1.75 (1.10–2.77)*
Model 2			
Calendar year	0.91 (0.86–0.96)*	0.92 (0.84–1.01)	0.91 (0.85–0.97)*
Diabetes (yes vs. no)	1.70 (1.32–2.16)*	1.66 (1.05–2.55)*	1.72 (1.27–2.30)*
Male vs. female	1.10 (0.97–1.26)	—	—
Age (years)†			
≥90	75.49 (57.79–98.63)*	63.36 (37.92–102.66)*	86.01 (61.32–121.84)*
80–89	44.99 (36.39–56.05)*	37.62 (26.94–53.14)*	51.75 (38.80–70.37)*
70–79	9.83 (7.75–12.53)*	8.91 (6.19–12.89)*	10.85 (7.81–15.26)*
60–69	3.61 (2.67–4.85)*	3.46 (2.20–5.35)*	3.78 (2.47–5.73)*
50–59	2.15 (1.55–2.95)*	1.96 (1.19–3.14)*	2.36 (1.49–3.67)*
Diabetes × calendar year	0.91 (0.82–1.02)	0.94 (0.78–1.14)	0.89 (0.78–1.02)

*$P < 0.05$. †Baseline: <50 years. ‡95% CI.

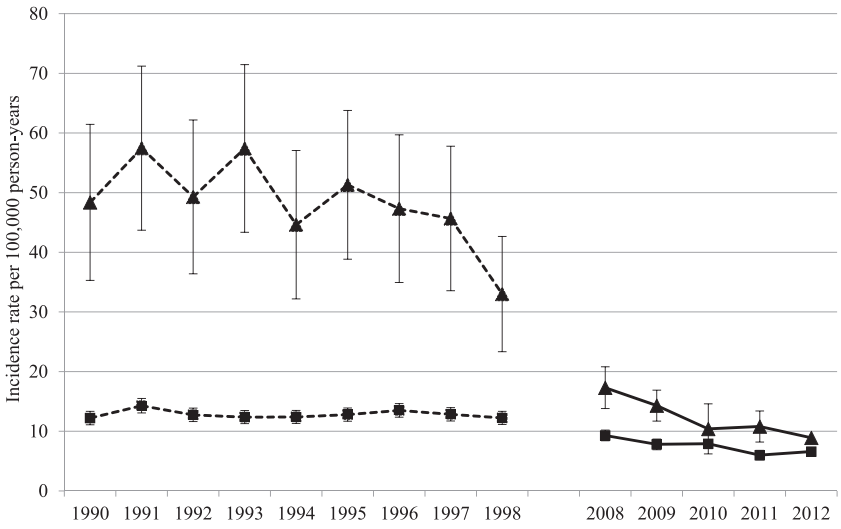

Figure 1—Time trend of age- and sex-standardized (standardized to the 2010 German population) incidence of blindness in the entire population and comparison with the previous examination. Black triangles, persons with diabetes; black squares, persons without diabetes; solid lines, study period of the recent examination analyzed in this study; dotted lines, study period of the previous examination.

and in the following years this treatment was established for patients with diabetic macular edema (ranibizumab in 2010 and aflibercept in 2014), retina vascular occlusion, and new vessels in pathologic myopia.

We found that the RR comparing persons with and persons without diabetes was higher among younger age-groups, with comparable results in both sexes. This result was in line with a previous study where the RR was increased among persons <60 years of age (5). This finding is not surprising, since with increasing age, risk of blindness strongly increased among persons without diabetes for other reasons (e.g., age-related macular degeneration, glaucoma). However, to the best of our knowledge no study found a significant decreased risk of blindness among persons with diabetes compared with those without diabetes among the elderly. A possible explanation could be that elderly persons with diabetes may be a selection of more healthy persons who survived, since mortality due to diabetes strongly increased in the study region in the elderly population (21). Furthermore, it could be assumed that the probability of a diabetes diagnosis rises strongly with age, leading to an increased denominator of incidence (11).

The definition of blindness is rather strict in Germany, making it difficult to compare incidences with other countries. Hall et al. (11) from Scotland showed a reduction for new blindness in the population with diabetes: the mean incidence of blindness attributable to diabetes was 42.7 per 100,000 person-years (95% CI 25–60) for 2000–2009 compared with 64.3 per 100,000 person-years for 1990–1999 (P = 0.062). The RR of developing blindness per year was 0.89 (95% CI 0.811–0.988; P = 0.028) for 2000–2009. The authors suggest that this may be a consequence of an increased denominator population, resulting from better recording of diabetes and changes to the diagnostic criteria. In Poland, the IR of blindness due to diabetes decreased significantly within the diabetic population from 102.4 per 100,000 (95% CI 65.7–139.0) in 1989 to 13.3 per 100,000 (3.8–24.9) in 2004 (10). However, the comparison of these studies is limited, since the IR was not adjusted for age or sex. Furthermore, no comparison with the IR in the population without diabetes was performed.

Limitations and Strengths

Several limitations have to be considered. Firstly, the considered districts of all analyses since the year 2008 were not exactly the same as the districts included in the analyses during the 1990s. Nevertheless, it was shown that the overall incidence of blindness was quite homogenous in this area (3). Secondly, the data are based on all newly registered blind persons in a limited geographic area during a certain period. There is no information about how many or which people do not apply for the blindness allowance even though they are entitled to. Thirdly, since 2005 the welfare authorities of municipalities are responsible for the blindness allowance procedure. Before 2005, the procedure was centralized in two state authorities. We cannot rule out that this change of responsibility influenced the acceptance of the blindness allowance. Fourthly, it is known that diabetes prevalence increased as a result of improved and earlier detection of the disease, which leads to a less severely diseased population with diabetes, resulting in a decrease in incidence of blindness. However, we also observed a similar decrease between 2008 and 2012 in the population without diabetes. Finally, only extreme, severe cases of blindness could be considered in our data. Therefore, we cannot rule out that the incidence of less severe visual impairment remained constant or even increased.

One of the strengths of our study is that the procedure of blindness allowance was based by law on administrative files of the welfare administration and has not changed for decades. Because of the amount of the blindness allowance, it can be expected that almost all incident cases continue to be recorded in this way. Furthermore, we have—despite the uncertainties mentioned above—an overview of a long period in one region where data were assessed using the same means. Overall, the reduction in the incidence of blindness may be substantial over the past three decades, and this may in part be due to improved diabetes care, as considered in the St. Vincent Declaration.

We found a significant reduction in IR of blindness in both the population with and that without diabetes, which, compared with the 1990s, was particularly strong among individuals with diabetes. These findings may be explained by effective secondary prevention therapies and improved ophthalmologic care beyond diabetic retinopathy, in particular with regard to macular degeneration, which means earlier detection of the diseases.

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Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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RESEARCH ARTICLE

Incidence and relative risk of stroke in the diabetic and the non-diabetic population between 1998 and 2014: A community-based stroke register

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Data Availability Statement: The data are subject to national data protection laws and only available upon formal request. The responsible database manager is Michael Weingärtner (Interdisciplinary Centre for Health Technology Assessment (HTA) and Public Health, Friedrich Alexander University of Erlangen-Nürnberg, Erlangen, Germany) who needs to be contacted at Michael.Weingaertner@uk-erlangen.de.

Abstract

One major objective of the St. Vincent Declaration was to reduce excess risk of stroke in people with diabetes mellitus. The aim of this study is to estimate the trend of incidence and relative risk of stroke in the diabetic and the non-diabetic populations in Germany over a 17-year period. We estimated age±sex standardised incidence rates of all stroke and ischaemic stroke in people with and without diabetes based on an ongoing prospective community-based stroke register covering 105,000 inhabitants. Time trends were analysed using Poisson regression. In total, 3,111 individuals (diabetes: 28.4%, men 46.9%, mean age 73.1 years (SD 13.2)) had a first stroke, 84.9% of which were ischaemic stroke. Among people with diabetes we observed a significant reduction in all stroke incidence by 1.5% per year (relative risk: 0.985; 95% confidence interval 0.972±0.9995) Likewise, this incidence tended to decrease for ischaemic stroke by 1% per year (0.993; 0.979±1.008). In contrast, the incidence rate for all stroke remained nearly stable among people without diabetes (1.003; 0.993±1.013) and for ischaemic stroke (1.002; 0.991±1.013). The relative risk comparing diabetic and non-diabetic population decreased for all stroke (two percent annual reduction) but not for ischaemic stroke. Time trends were similar for both sexes regarding all and ischaemic strokes. We found a reduction in risk of stroke in the diabetic population while this rate did not materially change in the non-diabetic population.

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Introduction

One of the primary objectives of the St. Vincent declaration was the decrease of stroke risk among persons with diabetes towards to that risk of the non-diabetic population [1, 2]. Several studies found an about two- to threefold elevated risk of stroke among individuals with diabetes compared to subjects without diabetes with particular high relative risks (RR) in the younger population [3–7].

However, only few studies evaluated the incidence rate (IR) of stroke in the diabetic compared with the non-diabetic population and their RRs. In a previous study analysing the IR of stroke in health insurance data for the years 2005–2007 in Germany [8], we found the IR of stroke in the diabetic population to be approximately double that in the non-diabetic population. However, no investigation of time trend could be considered due to the short time span.

Several studies from Western Europe and the USA indicate that the IR of stroke is declining [9–12]. However, it is unknown whether the decline has also been observed in people with diabetes or whether the gap between the diabetic and non-diabetic populations has narrowed. We found only two studies analysing trends of the IR of stroke in the diabetic compared with the non-diabetic population: Rautio and colleagues found declining IR of stroke in Sweden in non-diabetic men and women and diabetic women, but not in men with diabetes [13]. In Spain, Muñoz and colleagues found stable IR of haemorrhagic stroke in the diabetic population, whereas it decreased substantially in the non-diabetic population [14].

The objective of this study was to estimate the IR of stroke in the diabetic and the non-diabetic population as well as the RR and the investigation of time trends over a period of 17 years (1998–2014).

Materials and methods

Study population and data assessment

We analysed data from the Erlangen Stroke Project (ESPro), which is an ongoing prospective community-based stroke register in Germany covering a total population of 105,000 inhabitants. Since 1994, ESPro has been monitoring IR, risk factors, aetiology, and long-term outcome of stroke [15]. The characteristics of the study population, investigations and methods of assessment have been described in detail elsewhere [12, 16]. In brief, a number of sources with particularly overlapping information was applied to ensure complete case ascertainment as suggested as international gold-standard approach by Feigin et al. [17]. (1) hospital admission, computer-linked records systems and discharge lists; (2) regular checks of all relevant residential and hospital wards and nursing homes; (3) records of ambulance and emergency services; (4) death certificates and (5) general practitioners [16]. For the present study we included all hospitalised and non-hospitalised patients with suspected fatal or non-fatal stroke between 1 January 1998 and 31 December 2014.

A study clinician defined stroke diagnosis according to the criteria of the World Health Organization [18] and imaging. Patients with first-ever stroke (ischaemic stroke, intracerebral haemorrhage, subarachnoid haemorrhage, and stroke of uncertain cause) were included in the present study [19]. Persons with transient ischaemic attacks (TIA) were only registered but not further assessed and therefore excluded [16], since the WHO definition on stroke does not meet the criteria for TIA. We assessed IR of stroke (ischaemic strokes as subgroup analysis) with regard to age, sex, diabetes status, and date of the first stroke. Furthermore, we also described all incident cases with regard to smoking status, socioeconomic status (education), and comorbidities (myocardial infarction and hypertension).

A person was classified as having diabetes by 1) use of anti-hyperglycaemic drugs, 2) a fasting blood glucose level of 126 mg/dl and HbA1c >6.5 or above, and 3) self-report of physician-diagnosed diagnosis. The latter information was verified by checking the records of general practitioners and care protocols.

Data of the population of Erlangen were obtained from the Federal Office for Statistics [20]. The diabetic population was estimated in the adult population based on age- (18–39, 40–49, 50–59, 60–69, 70–79, and 80+ years) and sex-specific diabetes prevalence from two German nationwide surveys (German Health Interview and Examination Surveys (GNHIES98), DEGS1)) [21–23] conducted in 1997–99 and 2008–11 respectively. Diabetes was defined in both surveys based on self-report of physician-diagnosed diabetes, intake of antihyperglycaemic medication as well as an HbA1c value $\geq$ 6.5% within the last week before the survey [24]. The Robert Koch Institute regularly conducts health interview surveys as a part of its nationwide health monitoring. These two surveys are the only nationwide data sources with a comparable study design to estimate reliable age–sex specific diabetes prevalence covering more than a decade. As both surveys only covered the age range 18–79 years, we assumed that the estimated diabetes prevalence remained constant in the oldest age group (80+ years), which has been previously shown to be reliable [21].

We assumed that the estimated age- and sex-specific diabetes prevalence linearly increased from 1998 to 2011 using the estimators of GNHIES98 for the first and DEGS1 for the last year. We further assumed that the estimated diabetes prevalence continued to rise up to 2014 with the same increase.

Statistical analyses

The main analyses were conducted for the entire population as well as separately for men and women. We computed stratum-specific and age-sex standardised IRs of stroke with 95% CIs in the estimated population with and without diabetes for each calendar year using the German population of 2005 as standard population. The number of persons with diabetes was estimated by multiplying the estimated diabetes prevalence of each age and sex stratum with the corresponding study population of Erlangen. We calculated person years by taking the estimated number of persons with and without diabetes for each calendar year. Furthermore, we estimated RRs comparing diabetic versus non-diabetic populations from the standardized IRs.

In order to investigate time trends, we first performed separate Poisson regression models with IRs of all stroke as dependent variable for individuals with as well as without diabetes using year of stroke diagnosis as linear continuous difference from baseline year 1998 and age as independent variables. The two lowest age classes (i.e. 18–39, 40–49 years) were combined to one group (18–49 years) due to convergence problems of some models and were therefore used as reference group. Furthermore, we fitted analogous Poisson models to the entire population. In these models, we additionally included a variable presence of diabetes (yes vs. no) as well as an interaction term for diabetes and years since 1998.

In a sensitivity analysis, the main analyses were repeated assuming that the estimated age- and sex-specific diabetes prevalence remained constant for the years 2011–2014 since it was discussed whether the estimated diabetes prevalence remained constant or further increased in the later years. In order to take into account a potential misclassification bias due to first-ever all strokes with an unknown diabetes status, we further computed the main analyses, counting all these cases first as diabetic and second as non-diabetic.

The main analyses were also repeated for strokes due to ischaemic stroke.

To take into account over-dispersion of the outcome variable, all analyses were conducted with the de-scale adjustment [25], which was based on cumulated data on the covariate strata

year*sex*age class*diabetes. We performed analysis using the Statistical Analysis System SAS (SAS for Windows 7, Release 9.4 TS1M1, SAS Institute Inc. Cary, NC, USA).

ESPro was approved by the local ethics committee. Patients or their legal representatives gave their written informed consent for participation.

Results

Study population

The description of the study population is presented in Table 1. The data covered the adult ($\geq$ 18 years) population of Erlangen (1998: 83,584, 2014: 90,428). Diabetes prevalence in the Erlangen population increased from 5.6% in 1998 to 8.2% in 2014, with higher values in the female population.

In total, we identified 3,579 people with a first-ever stroke in the years 1998–2014. We excluded 468 individuals, as their diabetes status was not known. Of the remaining 3,111, 28.4% were classified as having diabetes (antihyperglycaemic drugs 74.6%; self-reports of physician-diagnosed diagnosis 15.6% and laboratory findings 9.7%). 53.1% were female with no consistent change in proportion over time. The mean age at the time of first-ever stroke was 73.1 years (standard deviation (SD) 13.2), which remained nearly stable over the time period, with higher values in women (75.8 years, SD 13.3) and individuals with diabetes (74.9 years, SD 10.6). At 84.9% ischaemic stroke was the most common stroke type followed by intercerebral haemorrhage (11.5%) and subarachnoidal haemorrhage (2.7%). These proportions remained nearly stable over the study period and were comparable among all subgroups.

Incidence rates and relative risks

Age–sex standardized IRs of all stroke for each year are shown in Figs 1–3. There were brief variations, which was particularly true in the population with diabetes (Fig 1). Over the whole study period, we observed a decrease in the IR per 100,000 person years in the population with diabetes (1998: 401.2 [95% confidence interval (CI) 279.4–523.1]; 2014: 238.5 [155.8–321.2]) with a particularly strong decrease in the last 3 years. This pattern was similar for both sexes with higher IRs in the male-population (Figs 2 and 3). In contrast, this IR remained nearly constant in the population without diabetes, with a moderate increase in the last 3 years (1998: 212.6 [174.5–250.6]; 2014: 235.2 [199.2–271.2]). With regard to the population with diabetes, higher IR were seen among men while these results were comparable for both sexes in the population without diabetes.

The RR of all stroke in the population with diabetes compared with the population without diabetes decreased over the whole study period and was highest in 2001 (RR: 2.4 [95% CI 1.6–3.6]) and lowest with no difference in 2014 (RR: 1.0 [0.7–1.5]). Th RR was somewhat higher among men in the first years of the study period while similar values were seen for the later years in both sexes (data not shown).

When repeating the analyses for ischaemic stroke (Figs 4–6), we observed only a slight decrease in IR per 100,000 person years in the population with diabetes (1998: 258.1 [179.7–336.4]; 2014: 209.4 [130.0–288.9]), while this IR remained nearly constant in the population without diabetes (1998: 190.4 [154.3–226.6]; 2014: 207.6 [173.8–241.5]). The RR ranged between 2.6 [1.7–4.1] in 2001 and 1.0 [0.7–1.5] in 2014. When stratifying for sex, we observed similar results despite increased variation of IRs, with higher IRs for men in the diabetic population.

Table 1. Description of persons with first stroke, and the background population, Erlangen, 1998–2014.

						men		women	
	total	men	women	diabetes	no diabetes	diabetes**	no diabetes**	diabetes**	no diabetes**
number of persons with first stroke (%*)	3,111 (100.0)	1,458 (46.9)	1,653 (53.1)	884 (28.4)	2,227 (71.6)	435 (29.8)	1,023 (70.2)	449 (27.2)	1,204 (72.8)
Person years (%)	1,481,658 (100.0)	718,669 (48.5)	762,989 (51.5)	101,456 (6.8)	1,380,202 (93.2)	43,641 (6.1)	675,028 (93.9)	57,815 (7.6)	705,174 (92.4)
Mean age*** (years, SD)	73.1 (13.2)	70.1 (12.5)	75.8 (13.3)	74.9 (10.6)	72.4 (14.0)	71.4 (10.3)	69.5 (13.3)	78.3 (9.8)	74.9 (14.2)
Age class									
18±39 (%)	60 (1.9)	23 (1.6)	37 (2.2)	1 (0.1)	59 (2.6)	0 (0.0)	23 (2.2)	1 (0.2)	36 (3.0)
40±49 (%)	140 (4.5)	77 (5.3)	63 (3.8)	19 (2.1)	121 (5.4)	14 (3.2)	63 (6.2)	5 (1.1)	58 (4.8)
50±59 (%)	292 (9.4)	196 (13.4)	96 (5.8)	65 (7.4)	227 (10.2)	47 (10.8)	149 (14.6)	18 (4.0)	78 (6.5)
60±69 (%)	571 (18.4)	352 (24.1)	219 (13.2)	171 (19.3)	400 (18.0)	120 (27.6)	232 (22.7)	51 (11.4)	168 (14.0)
70±79 (%)	973 (31.3)	474 (32.5)	499 (30.2)	322 (36.4)	651 (29.2)	161 (37.0)	313 (30.6)	161 (35.9)	338 (28.1)
$\geq$ 80 (%)	1,075 (34.6)	336 (23.0)	739 (44.7)	306 (34.6)	769 (34.5)	93 (21.4)	243 (23.8)	213 (47.4)	526 (43.7)
Smoking status									
Smoker (%)	542 (17.4)	329 (22.6)	213 (12.9)	146 (16.5)	396 (17.8)	101 (23.2)	228 (22.3)	45 (10.0)	168 (14.0)
Ex-smoker (%)	612 (19.7)	469 (32.2)	143 (8.7)	179 (20.2)	433 (19.4)	145 (33.3)	324 (31.7)	34 (7.6)	109 (9.1)
Non-smoker (%)	767 (24.7)	237 (16.3)	530 (32.1)	191 (21.6)	576 (25.9)	64 (14.7)	173 (16.9)	127 (28.3)	403 (33.5)
Unknown (%)	1,190 (38.3)	423 (29.0)	767 (46.4)	368 (41.6)	822 (36.9)	125 (28.7)	298 (29.1)	243 (54.1)	524 (43.5)
Highest degree of education									
No graduation (%)	60 (1.9)	27 (1.9)	33 (2.0)	16 (1.8)	44 (2.0)	7 (1.6)	20 (2.0)	9 (2.0)	24 (2.0)
Primary school (%)	1,173 (37.7)	497 (34.1)	676 (40.9)	357 (40.4)	816 (36.6)	160 (36.8)	337 (32.9)	197 (43.9)	479 (39.8)
Secondary school (%)	456 (14.7)	214 (14.7)	242 (14.6)	114 (12.9)	342 (15.4)	64 (14.7)	150 (14.7)	50 (11.1)	192 (15.9)
Baccalaureate (%)	172 (5.5)	89 (6.1)	83 (5.0)	36 (4.1)	136 (6.1)	26 (6.0)	63 (6.2)	10 (2.2)	73 (6.1)
University (%)	365 (11.7)	295 (20.2)	70 (4.2)	76 (8.6)	289 (13.0)	67 (15.4)	228 (22.3)	9 (2.0)	61 (5.1)
Unknown (%)	885 (28.4)	336 (23.0)	549 (33.2)	285 (32.2)	600 (26.9)	111 (25.5)	225 (22.0)	174 (38.8)	375 (31.1)
Diagnosis of myocardial infarction									
Yes (%)	289 (9.3)	177 (12.1)	112 (6.8)	102 (11.5)	187 (8.4)	69 (15.9)	108 (10.6)	33 (7.3)	79 (6.6)
No (%)	2,499 (80.3)	1,148 (78.7)	1,351 (81.7)	666 (75.3)	1,833 (82.3)	319 (73.3)	829 (81.0)	347 (77.3)	1,004 (83.4)
Unknown (%)	323 (10.4)	133 (9.1)	190 (11.5)	116 (13.1)	207 (9.3)	47 (10.8)	86 (8.4)	69 (15.4)	121 (10.0)
Diagnosis of hypertension									
Yes (%)	2,357 (75.8)	1,085, (74.4)	1,272, (77)	777 (87.9)	1,580 (70.9)	376 (86.4)	709 (69.3)	401 (89.3)	871 (72.3)
No (%)	109 (3.5)	54, (3.7)	55 (3.3)	22 (2.5)	87 (3.9)	11 (2.5)	43 (4.2)	11 (2.4)	44 (3.7)
Unknown (%)	645 (20.7)	319, (21.9)	326 (19.7)	85 (9.6)	560 (25.1)	48 (11.0)	271 (26.5)	37 (8.2)	289 (24.0)
Number of first strokes by type									
Ischaemic stroke (%)	2,640 (84.9)	1,240 (85)	1,400 (84.7)	775 (87.7)	1,865 (83.7)	379 (87.1)	861 (84.2)	396 (88.2)	1,004 (83.4)
Intracerebral haemorrhage (%)	357 (11.5)	178 (12.2)	179 (10.8)	87 (9.8)	270 (12.1)	48 (11.0)	130 (12.7)	39 (8.7)	140 (11.6)
Subarachnoid haemorrhage (%)	85 (2.7)	31 (2.1)	54 (3.3)	9 (1.0)	76 (3.4)	4 (0.9)	27 (2.6)	5 (1.1)	49 (4.1)
Stroke of uncertain cause (%)	29 (0.9)	9 (0.6)	20 (1.2)	13 (1.5)	16 (0.7)	4 (0.9)	5 (0.5)	9 (2.0)	11 (0.9)
Number of first strokes per year									

(*Continued*)

Table 1. (*Continued*)

						men		women	
	total	men	women	diabetes	no diabetes	diabetes**	no diabetes**	diabetes**	no diabetes**
1998 (%*)	179 (100.0)	72 (40.2)	107 (59.8)	57 (31.8)	122 (68.2)	27 (37.5)	45 (62.5)	30 (28.0)	77 (72.0)
1999 (%*)	192 (100.0)	97 (50.5)	95 (49.5)	62 (32.3)	130 (67.7)	34 (35.1)	63 (64.9)	28 (29.5)	67 (70.5)
2000 (%*)	172 (100.0)	81 (47.1)	91 (52.9)	50 (29.1)	122 (70.9)	19 (23.5)	62 (76.5)	31 (34.1)	60 (65.9)
2001 (%*)	141 (100.0)	64 (45.4)	77 (54.6)	53 (37.6)	88 (62.4)	22 (34.4)	42 (65.6)	31 (40.3)	46 (59.7)
2002 (%*)	141 (100.0)	76 (53.9)	65 (46.1)	43 (30.5)	98 (69.5)	21 (27.6)	55 (72.4)	22 (33.8)	43 (66.2)
2003 (%*)	158 (100.0)	63 (39.9)	95 (60.1)	44 (27.8)	114 (72.2)	20 (31.7)	43 (68.3)	24 (25.3)	71 (74.7)
2004 (%*)	193 (100.0)	80 (41.5)	113 (58.6)	44 (22.8)	149 (77.2)	21 (26.3)	59 (73.8)	23 (20.4)	90 (79.6)
2005 (%*)	216 (100.0)	101 (46.8)	115 (53.2)	55 (25.5)	161 (74.5)	27 (26.7)	74 (73.3)	28 (24.3)	87 (75.7)
2006 (%*)	181 (100.0)	81 (44.8)	100 (55.2)	51 (28.2)	130 (71.8)	19 (23.5)	62 (76.5)	32 (32.0)	68 (68.0)
2007 (%*)	169 (100.0)	89 (52.7)	80 (47.3)	41 (24.3)	128 (75.7)	24 (27.0)	65 (73.0)	17 (21.3)	63 (78.8)
2008 (%*)	176 (100.0)	92 (52.3)	84 (47.7)	52 (29.5)	124 (70.5)	28 (30.4)	64 (69.6)	24 (28.6)	60 (71.4)
2009 (%*)	166 (100.0)	68 (41.0)	98 (59.0)	49 (29.5)	117 (70.5)	23 (33.8)	45 (66.2)	26 (26.5)	72 (73.5)
2010 (%*)	192 (100.0)	86 (44.8)	106 (55.2)	58 (30.2)	134 (69.8)	22 (25.6)	64 (74.4)	36 (34.0)	70 (66.0)
2011 (%*)	199 (100.0)	89 (44.7)	110 (55.3)	63 (31.7)	136 (68.3)	34 (38.2)	55 (61.8)	29 (26.4)	81 (73.6)
2012 (%*)	193 (100.0)	98 (50.8)	95 (49.2)	51 (26.4)	142 (73.6)	32 (32.7)	66 (67.3)	19 (20.0)	76 (80.0)
2013 (%*)	218 (100.0)	114 (52.3)	104 (47.7)	58 (26.6)	160 (73.4)	34 (29.8)	80 (70.2)	24 (23.1)	80 (76.9)
2014 (%*)	225 (100.0)	107 (47.6)	118 (52.4)	53 (23.6)	172 (76.4)	28 (26.2)	79 (73.8)	25 (21.2)	93 (78.8)
Number of person years per year									
1998 (%*)	83,584	40,183 (48.1)	43,401 (51.9)	4,643 (5.6)	78,941 (94.4)	1,887 (4.7)	38,296 (95.3)	2,756 (6.4)	40,645 (93.6)
1999 (%*)	83,760	40,309 (48.1)	43,451 (51.9)	4,798 (5.7)	78,962 (94.3)	1,958 (4.9)	38,351 (95.1)	2,840 (6.5)	40,611 (93.5)
2000 (%*)	83,932	40,383 (48.1)	43,549 (51.9)	4,969 (5.9)	78,963 (94.1)	2,035 (5.0)	38,348 (95.0)	2,934 (6.7)	40,615 (93.3)
2001 (%*)	84,980	40,993 (48.2)	43,987 (51.8)	5,150 (6.1)	79,830 (93.9)	2,126 (5.2)	38,867 (94.8)	3,024 (6.9)	40,963 (93.1)
2002 (%*)	85,198	41,086 (48.2)	44,112 (51.8)	5,277 (6.2)	79,921 (93.8)	2,199 (5.4)	38,887 (94.6)	3,078 (7.0)	41,034 (93.0)
2003 (%*)	85,436	41,259 (48.3)	44,177 (51.7)	5,413 (6.3)	80,023 (93.7)	2,278 (5.5)	38,981 (94.5)	3,135 (7.1)	41,042 (92.9)
2004 (%*)	85,704	41,355 (48.3)	44,349 (51.7)	5,591 (6.5)	80,113 (93.5)	2,370 (5.7)	38,985 (94.3)	3,221 (7.3)	41,128 (92.7)
2005 (%*)	86,222	41,711 (48.4)	44,511 (51.6)	5,732 (6.6)	80,490 (93.4)	2,448 (5.9)	39,263 (94.1)	3,284 (7.4)	41,227 (92.6)
2006 (%*)	86,905	42,038 (48.4)	44,867 (51.6)	5,911 (6.8)	80,994 (93.2)	2,540 (6.0)	39,498 (94.0)	3,371 (7.5)	41,496 (92.5)
2007 (%*)	87,830	42,584 (48.5)	45,246 (51.5)	6,108 (7.0)	81,722 (93.0)	2,641 (6.2)	39,943 (93.8)	3,467 (7.7)	41,779 (92.3)
2008 (%*)	88,182	42,858 (48.6)	45,324 (51.4)	6,279 (7.1)	81,903 (92.9)	2,730 (6.4)	40,128 (93.6)	3,549 (7.8)	41,775 (92.2)
2009 (%*)	88,745	43,128 (48.6)	45,617 (51.4)	6,464 (7.3)	82,281 (92.7)	2,822 (6.5)	40,306 (93.5)	3,642 (8.0)	41,975 (92.0)
2010 (%*)	88,978	43,239 (48.6)	45,739 (51.4)	6,645 (7.5)	82,333 (92.5)	2,925 (6.8)	40,314 (93.2)	3,720 (8.1)	42,019 (91.9)
2011 (%*)	90,888	44,506 (49.0)	46,382 (51.0)	6,873 (7.6)	84,015 (92.4)	3,042 (6.8)	41,464 (93.2)	3,831 (8.3)	42,551 (91.7)
2012 (%*)	90,307	44,231 (49.0)	46,076 (51.0)	7,013 (7.8)	83,294 (92.2)	3,111 (7.0)	41,120 (93.0)	3,902 (8.5)	42,174 (91.5)

(*Continued*)

Table 1. (*Continued*)

						men		women	
	total	men	women	diabetes	no diabetes	diabetes**	no diabetes**	diabetes**	no diabetes**
2013 (%*)	90,579	44,423 (49.0)	46,156 (51.0)	7,210 (8.0)	83,369 (92.0)	3,220 (7.2)	41,203 (92.8)	3,990 (8.6)	42,166 (91.4)
2014 (%*)	90,428	44,383 (49.1)	46,045 (50.9)	7,380 (8.2)	83,048 (91.8)	3,309 (7.5)	41,074 (92.5)	4,071 (8.8)	41,974 (91.2)

* Percentages related to all persons with first stroke.

** Percentages related to total male population and female population, respectively.

*** Age at time of first stroke.

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Analysis of time trend

Table 2 shows results of the incidence trend from the fully adjusted Poisson models. The RRs in the population with and without diabetes are shown in models 1a and 1b. During the observation period we observed a significant decrease of all stroke incidence, by one and a half percent per year (RR per calendar year: 95% CI: 0.985; 0.972–0.9995), in the population with diabetes, with similar results among men and women with the exception that these trends were not significant due to a smaller sample size. In contrast, the trend of incidence remained constant among individuals without diabetes (RR per calendar year 1.003; 0.993–1.013), which was true for both sexes. When considering the entire population in model 2 we observed a significant increased IR in the population with diabetes compared with the population without diabetes. This difference was particularly strong among the younger age groups but was not significant in the oldest age group (RR diabetes vs. no diabetes < 50 years: 3.43; 2.09–5.61; 80 + years: 1.11; 0.98–1.27) (data not shown). The interaction diabetes*calendar year was significant, indicating that this RR decreased by two percent per year (RR per calendar year 0.979; 0.960–0.997) with similar results in both sexes (model 2). These results did not alter when

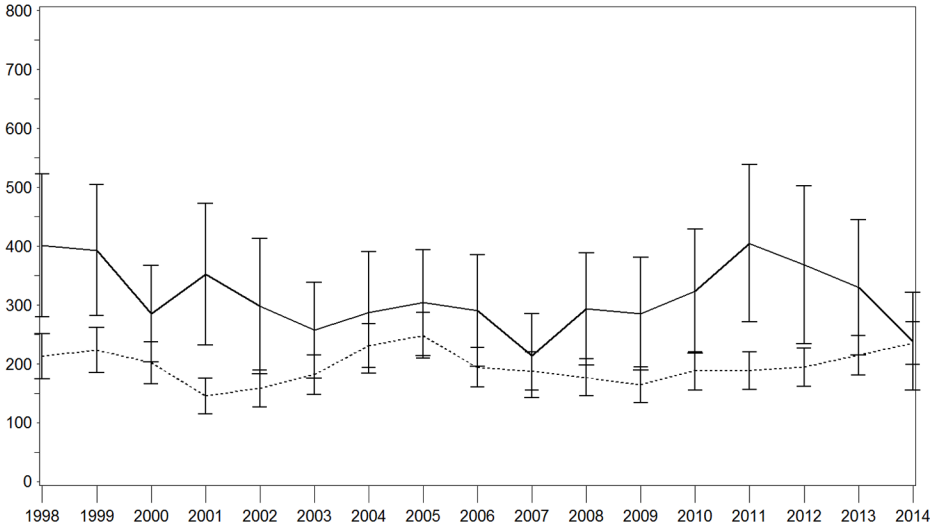

Fig 1. Age–sex standardised incidence rate of stroke with and without diabetes in the total population. Continuous lines = persons with diabetes; dotted lines = persons without diabetes; x-axis: calendar year; y-axis: incidence rate per 100,000 person years.

https://doi.org/10.1371/journal.pone.0188306.g001

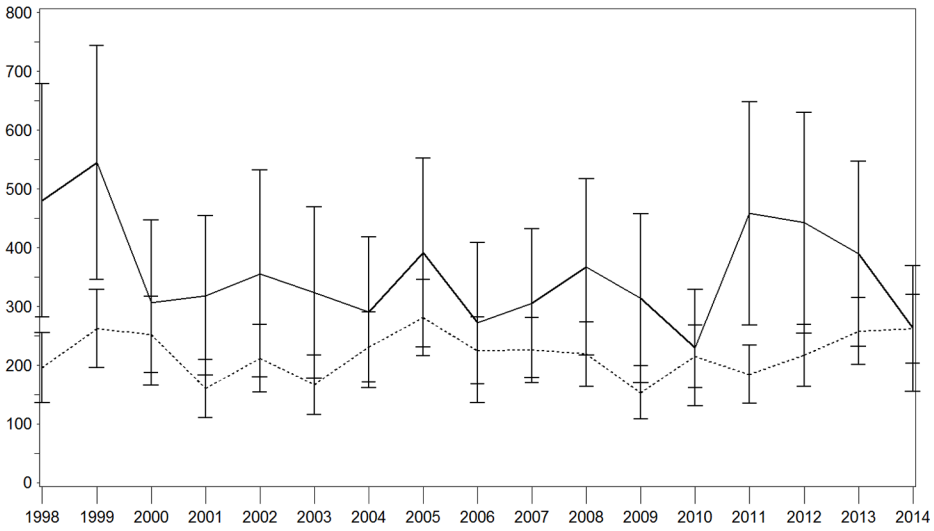

Fig 2. Age–sex standardised incidence rate of stroke with and without diabetes in the male population. Continuous lines = persons with diabetes; dotted lines = persons without diabetes; x-axis: calendar year; y-axis: incidence rate per 100,000 person years.

https://doi.org/10.1371/journal.pone.0188306.g002

assuming a constant estimated diabetes prevalence from 2011 (S1 Fig, S1 Table). Likewise, the results regarding time trend did not materially change when counting all strokes with unknown diabetes first as diabetic (S2 Fig, S2 Table) and second as non-diabetic cases (S3 Fig, S3 Table).

For ischaemic stroke, we observed a slight but no significant decrease in IR in the population with diabetes by one percent per year, (RR per calendar year 0.993; 0.979–1.008) with comparable results among men and women. Likewise, this IR remained nearly constant among people without diabetes (1.003; 0.992–1.014), with similar results for both sexes. The

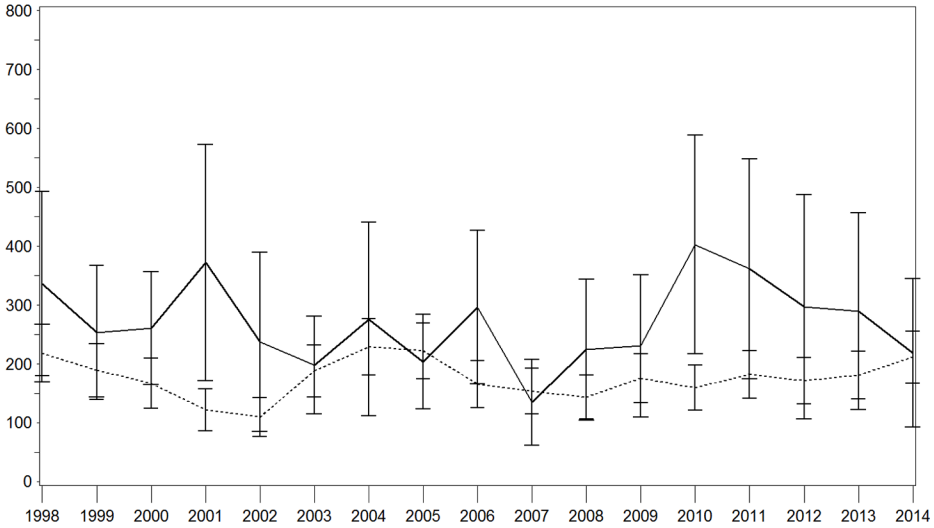

Fig 3. Age–sex standardised incidence rate of stroke with and without diabetes in the female population. Continuous lines = persons with diabetes; dotted lines = persons without diabetes; x-axis: calendar year; y-axis: incidence rate per 100,000 person years.

https://doi.org/10.1371/journal.pone.0188306.g003

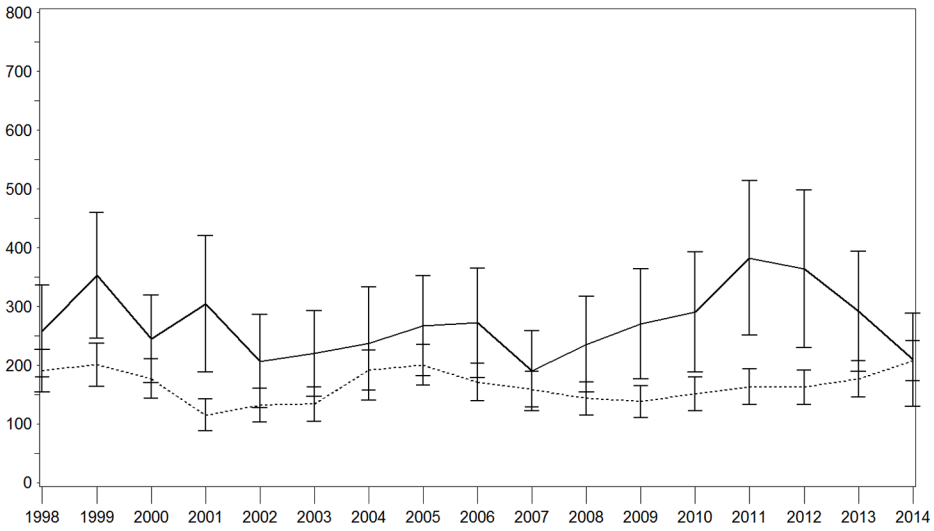

Fig 4. Age–sex standardised incidence rate of ischaemic stroke with and without diabetes in the total population. Continuous lines = persons with diabetes; dotted lines = persons without diabetes; x-axis: calendar year; y-axis: incidence rate per 100,000 person years.

https://doi.org/10.1371/journal.pone.0188306.g004

interaction diabetes*calendar year tended to decrease, however, was not significant, (0.987; 0.967–1.006), which was true for both sexes.

Discussion

Main findings

Our study is part of an evaluation of how well the St. Vincent objectives have been met in Germany. In our study region over the 17-year study period, we found a significant decrease in the IR of all stroke in the diabetic population. Considering solely ischaemic stroke in the

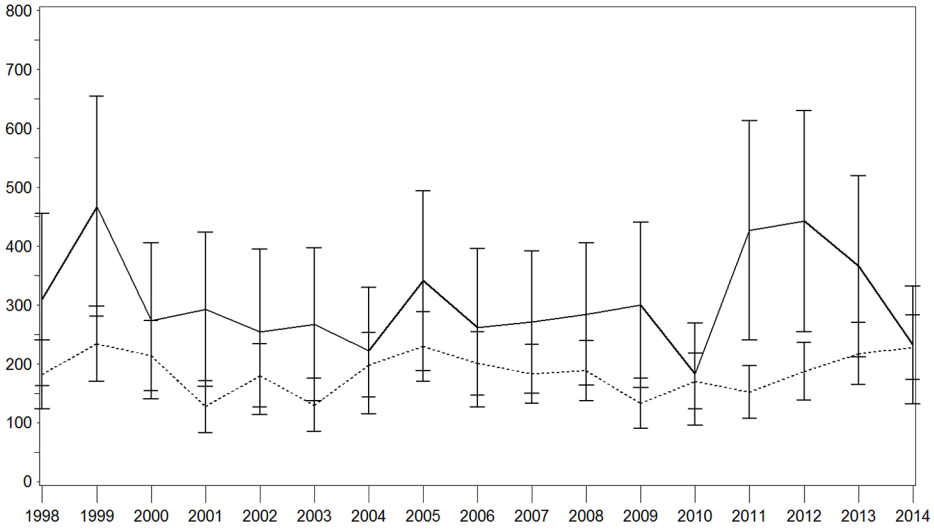

Fig 5. Age–sex standardised incidence rate of ischaemic stroke with and without diabetes in the male population. Continuous lines = persons with diabetes; dotted lines = persons without diabetes; x-axis: calendar year; y-axis: incidence rate per 100,000 person years.

https://doi.org/10.1371/journal.pone.0188306.g005

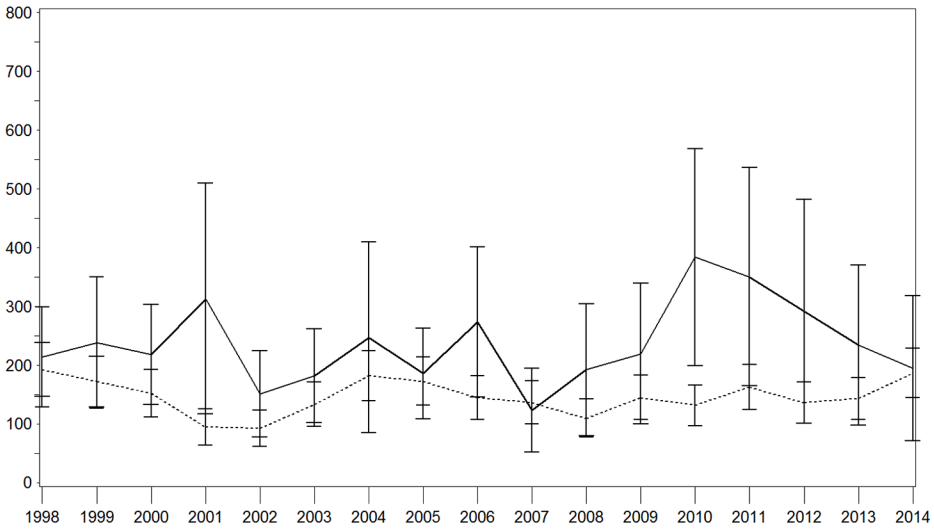

Fig 6. Age–sex standardised incidence rate of ischaemic stroke with and without diabetes in the female population. Continuous lines = persons with diabetes; dotted lines = persons without diabetes; x-axis: calendar year; y-axis: incidence rate per 100,000 person years.

https://doi.org/10.1371/journal.pone.0188306.g006

diabetic population, the risk tended to decrease, however, not significantly, maybe due to low statistical power. No change was found in the non-diabetic population with regard to all and ischaemic stroke.

Our findings may indicate an improvement in diabetes care. Several health technologies have been introduced in the past decades, such as medication to reduce hypertension, one of the most important risk factors of stroke. National programmes designed to improve diabetes care, e.g. disease management programmes, have been implemented since the beginning of the 2000s. The National Health Surveys found substantially improvements between 1997 and 2011, e.g. regarding the proportions of people with diabetes achieving an HbA_{1c} <7.0% (32.4% vs 65.4%), a blood pressure <130/80 mmHg (32.0% vs. 47.2%.), total cholesterol <190 mg/dl (13.5% vs. 41.9%), with statin use (11.7% vs. 35.9%), eye (51.1% vs. 78.4%), and foot (48.0% vs. 61.4%) examination within past 12 months [26]. However, other explanations may be possible. For example, it may be that the characteristics of the background population changed due to migration. Furthermore, general stroke prevention interventions in Erlangen may have changed the stroke population.

Comparison with other studies

We identified only two studies that analysed trends in the IR and RR of all stroke in the diabetic compared with the non-diabetic population. A Spanish study was restricted to haemorrhagic strokes [14]. Rautio and colleagues analysed all strokes and found declining stroke IRs in Sweden in non-diabetic men and women and diabetic women, but not in men with diabetes [13]. They did not find an explanation for this gender difference. Interestingly, in the Swedish region, the trend in the risk of myocardial infarction was also worse in diabetic men [13], and this was also observed in a German study [27]. In contrast, we did not find gender differences with regard to trend. Further studies are needed which look for gender differences in more detail.

Strengths and limitations

A number of limitations have to be considered. First, the results of our study are dependent on the estimates of the number of diabetic individuals in the background population. We

Table 2. Results of Poisson models*: Relative risks for Stroke, Erlangen, 1998–2014.

variables	relative risk for stroke (95% CI)		
All strokes	**total population**	**men**	**women**
Model 1a (persons with diabetes)			
Calendar year	0.985 (0.972±0.9995)**	0.987 (0.968±1.007)	0.985 (0.967±1.004)
Male vs. female	1.254 (1.089±1.443)**	---------	---------
Age (years)***			
≥ 80	17.963 (11.209±28.787)**	9.847 (5.620±17.254)**	34.681 (15.436±77.920)**
70±79	10.976 (6.856±17.573)**	7.907 (4.586±13.631)**	18.118 (8.034±40.857)**
60±69	6.600 (4.071±10.701)**	5.348 (3.080±9.288)**	8.509 (3.657±19.803)**
50±59	4.410 (2.613±7.443)**	3.084 (1.701±5.591)**	7.528 (2.994±18.929)**
Model 1b (persons without diabetes)			
Calendar year	1.003 (0.993±1.013)	1.003 (0.991±1.016)	1.003 (0.989±1.017)
Male vs. female	1.233 (1.117±1.361)**	---------	---------
Age (years)***			
≥ 80	56.831 (46.908±68.853)**	56.607 (44.655±71.758)**	51.784 (39.893±67.218)**
70±79	28.096 (23.134±34.121)**	33.575 (26.680±42.252)**	23.170 (17.660±30.399)**
60±69	12.637 (10.274±15.542)**	17.187 (13.542±21.812)**	8.918 (6.607±12.037)**
50±59	5.462 (4.340±6.875)**	7.947 (6.154±10.263)**	3.35 (2.345±4.786)**
Model 2			
Calendar year	1.004 (0.994±1.014)	1.005 (0.991±1.018)	1.003 (0.990±1.017)
Diabetes (yes vs. no)	1.728 (1.442±2.065)**	1.890 (1.480±2.401)**	1.558 (1.227±1.969)**
Male vs. female	1.250 (1.149±1.359)**	---------	---------
Age (years)***			
≥ 80	49.507 (41.477±59.503)**	44.855 (35.318±57.543)**	48.946 (38.780±62.644)**
70±79	26.091 (21.840±31.382)**	29.189 (23.190±37.158)**	22.956 (18.059±29.561)**
60±69	12.729 (10.552±15.442)**	16.342 (12.903±20.914)**	9.205 (7.062±12.106)**
50±59	5.776 (4.680±7.148)**	7.738 (5.987±10.073)**	3.768 (2.739±5.179)**
Diabetes x calendar year	0.979 (0.960±0.997)**	0.977 (0.953±1.001)	0.981 (0.956±1.006)
Ischaemic strokes only	total population	men	women
Model 1a (persons with diabetes)			
Calendar year	0.993 (0.979±1.008)	0.999 (0.978±1.020)	0.990 (0.971±1.010)
Male vs. female	1.235 (1.068±1.426)**	---------	---------
Age (years)***			
≥ 80	20.034 (12.099±33.173) **	11.671 (6.258±21.767)**	36.452 (15.489±85.786)**
70±79	11.935 (7.212±19.752) **	8.481 (4.607±15.614)**	19.398 (8.214±45.809)**
60±69	7.269 (4.338±12.181) **	5.764 (3.106±10.696)**	9.701 (3.991±23.579)**
50±59	4.801 (2.751±8.378) **	3.527 (1.824±6.819)**	7.072 (2.643±18.922)**
Model 1b (persons without diabetes)			
Calendar year	1.002 (0.991±1.013)	1.003 (0.990±1.017)	1.002 (0.986±1.017)
Male vs. female	1.260 (1.132±1.403)**	---------	---------
Age (years)***			
≥ 80	71.647 (57.228±89.699) **	66.994 (50.982±88.035)**	69.234 (50.261±95.369)**
70±79	35.007 (27.892±43.937) **	38.631 (29.595±50.426)**	31.070 (22.328±43.236)**
60±69	15.031 (11.810±19.129) **	19.411 (14.732±25.577)**	11.041 (7.686±15.862)**
50±59	6.174 (4.723±8.070) **	8.601 (6.395±11.569)**	3.840 (2.496±5.908)**
Model 2			
Calendar year	1.003 (0.992±1.014)	1.005 (0.990±1.019)	1.002 (0.988±1.017)
Diabetes (yes vs. no)	1.655 (1.364±2.001)**	1.751 (1.341±2.273)**	1.533 (1.186±1.971)**

(*Continued*)

Table 2. (*Continued*)

variables	relative risk for stroke (95% CI)		
All strokes	**total population**	**men**	**women**
Male vs. female	1.266 (1.157±1.385)**	---------	---------
Age (years)***			
≥ 80	61.328 (50.088±75.843)**	53.227 (40.744±70.529)**	63.936 (48.429±86.265)**
70±79	31.829 (25.969±39.397)**	33.003 (25.461±43.446)**	30.234 (22.748±41.020)**
60±69	15.105 (12.197±18.864)**	18.294 (14.017±24.219)**	11.614 (8.512±16.099)**
50±59	6.559 (5.163±8.372)**	8.521 (6.386±11.489)**	4.281 (2.937±6.252)**
Diabetes x calendar year	0.987 (0.967±1.006)	0.988 (0.962±1.015)	0.986 (0.960±1.013)

*Models were adjusted for all variables included in this table.

**p-value < 0.05.

***Baseline: 18±49 years.

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estimated diabetes prevalence using well-designed German health surveys, and performed sensitivity analyses, which resulted in stable estimates. In both surveys, diagnosed diabetes (GNHIES98, DEGS1) was uniformly defined by self-report of physician-diagnosed diagnosis, intake of antihyperglycaemic medication as well as an HbA1c value ≥ 6.5% within the last week before the survey [24]. Therefore, the definition of diabetes is not exactly the same as the case definition, however, quite similar. Our approach to estimate the background diabetic population using survey data has often been applied [28–30]. Unfortunately, we cannot exclude misclassification resulting in biased estimates of the IR and the RR. However, this was true for the whole observation period, hence, the time trend should not be affected. Second, we did not include clinical variables (e. g. population influx, changes of the provision of care considering stroke), since these data are missing for the background population. Third and last, we analysed data from a small region in Germany; however, the incidence figures were well comparable to a nationwide study 2005–2007 using statutory health insurance data [8].

The strengths of our study are that we could use a well-established population-based register and cover a long time span of 17 years. Furthermore, during the whole observation period 1998–2014 the method of case ascertainment, diagnostics definitions and techniques remained unchanged. Third, we were able to consider undetected diabetes in cases as well as in the background population.

Conclusion

With regard to the objectives of the St. Vincent declaration, we found a substantial reduction in the IR of all stroke in the diabetic population which also tended do decrease for ischaemic stroke. In contrast, the IR did not materially change in the non-diabetic population with regard to all and ischaemic stroke This may indicate an improvement in diabetes care. However, future research in other populations is needed to confirm these findings.

Supporting information

S1 Fig. Age–sex standardised incidence rate of stroke with and without diabetes (per 100,000 person years): Assuming the diabetes prevalence to be constant up to 2011. Continuous lines = persons with diabetes; dotted lines = persons without diabetes; x-axis: calendar year; y-axis: incidence rate per 100,000 person years.
(TIF)

S2 Fig. Age–sex standardised incidence rate of stroke with and without diabetes (per 100,000 person years): Assuming all first strokes with unknown diabetes status to be diabetic. Continuous lines = persons with diabetes; dotted lines = persons without diabetes; x-axis: calendar year; y-axis: incidence rate per 100,000 person years.
(TIF)

S3 Fig. Age–sex standardised incidence rate of stroke with and without diabetes (per 100,000 person years): Assuming all first strokes with unknown diabetes status to be non-diabetic. Continuous lines = persons with diabetes; dotted lines = persons without diabetes; x-axis: calendar year; y-axis: incidence rate per 100,000 person years.
(TIF)

S1 Table. Results of poisson models: Relative risks for stroke, Erlangen, 1998–2014: Assuming the diabetes prevalence to be constant up to 2011.
(DOCX)

S2 Table. Results of poisson models: Relative risks for stroke, Erlangen, 1998–2014: Assuming all first strokes with unknown diabetes status to be diabetic.
(DOCX)

S3 Table. Results of poisson models: Relative risks for stroke, Erlangen, 1998–2014: Assuming all first strokes with unknown diabetes status to be non-diabetic.
(DOCX)

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ARTICLE

Incidence and relative risk of renal replacement therapy in people with and without diabetes between 2002 and 2016 in a German region

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Abstract

Aims/hypothesis Data on trends of end-stage renal disease among people with diabetes are lacking. We analysed the incidence of end-stage renal disease, defined as renal replacement therapy, among people with and without diabetes, and the corresponding relative risk. Moreover, we investigated time trends for the period 2002–2016.

Methods In this retrospective population-based study we analysed data from one dialysis centre of a region in Germany covering a population of about 310,000 inhabitants. We estimated the age- and sex-standardised incidence rates for chronic renal replacement therapy among adults with and without diabetes and the corresponding relative risks. The time trend was analysed using Poisson regression models.

Results Between 2002 and 2016, 1107 people (61.2% male; mean age 71.6 years; 48.7% with diabetes) had a first renal replacement therapy. During the study period, the incidence rate in the population with diabetes varied from 93.6 (95% CI 50.4, 136.7) in 2002 to 140.5 (95% CI 80.6, 200.4) in 2016 per 100,000 person-years. In the population without diabetes the incidence rate was substantially lower and reached 17.3 (95% CI 10.9, 23.6) in 2002 and 24.6 (95% CI 17.5, 31.7) in 2009. The relative risk comparing people with and without diabetes was 3.57 (95% CI 3.09, 4.13). No significant change in the incidence rates was found during the observation period, either in the population with or in the population without diabetes, and thus the relative risk also remained constant.

Conclusions/interpretation People with diabetes have a higher risk of needing renal replacement therapy than those without diabetes, a fact that remained constant over a time period of 15 years.

Keywords Diabetes · End-stage renal disease · Epidemiology · Incidence · Renal replacement therapy

Maria Narres and Heiner Claessen are joint first authors and contributed equally.

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Research in context

What is already known about this subject?

- Individuals with diabetes starting renal replacement therapy (RRT) have poorer survival rates and higher treatment costs compared with people without diabetes
- Only a few population-based studies have investigated the incidence and temporal trends of RRT in the population with diabetes compared with the population without diabetes
- Results concerning time trends in the incidence of RRT in people with and without diabetes are contradictory

What is the key question?

- How did the incidence of RRT in people with and without diabetes in Germany change during the period 2002–2016?

What are the new findings?

- Incidence of RRT remained substantially higher among people with diabetes compared with people without diabetes, with an almost fourfold increased risk
- Incidence of RRT remained constant over the time period of 15 years in people both with and without diabetes
- Men had twice as high a risk of needing RRT compared with women

How might this impact on clinical practice in the foreseeable future?

- These results will be useful for practitioners, epidemiologists and healthcare planners when discussing the quality of diabetes care

Abbreviations

ESRD	End-stage renal disease
IR	Incidence rate
PY	Person-years
RRT	Renal replacement therapy

Introduction

The increasing prevalence of diabetes mellitus worldwide [1] leads to an increase in the number of people with complications of diabetes, including diabetic nephropathy and its last stage, end-stage renal disease (ESRD) requiring renal replacement therapy (RRT). Among people starting RRT, the proportion of individuals with diabetes (as comorbidity) ranges between 28% [2] and 51% [3]. Individuals with diabetes and ESRD have poorer survival rates than people without diabetes [2, 4–6]. Moreover, this group of individuals brings about especially high treatment costs [7, 8]. Nevertheless, there are only a few population-based studies that have analysed the incidence of RRT in the population with diabetes compared with the population without diabetes, in particular where diabetes was taken into account as a comorbidity and not only diabetic nephropathy as a primary kidney disease leading to ESRD [3, 4, 9–11]. In our previous study we analysed the incidence of RRT in 2002–2008 in a German region stratified by diabetes status [9]. In this study, no temporal change regarding the incidence of RRT could be detected among people either with or without diabetes. However, the considered time period of this study was quite short. Furthermore, a national guideline was implemented in 2010 in Germany addressing treatment and healthcare of adult individuals with diabetes and renal disease [12]. This may have improved diabetes care in this patient group.

The aims of this study were: (1) to analyse the incidence of RRT among individuals with and without diabetes as well as relative risk (RR) and (2) to investigate the corresponding time trends for the period 2002–2016.

Methods

Study design and data assessment The data analysed were sourced from one dialysis centre, which delivers dialysis to all inhabitants in a region in North Rhine-Westphalia, Western Germany (district of Mettmann excluding the cities of Ratingen, Monheim and Langenfeld), covering a population of about 310,000 inhabitants. As there is only this one dialysis centre in the region, it was assumed that nearly all individuals with RRT living in this region are treated there. This study was designed as a retrospective population-based study.

Study population A census-based description of the general population of the study region was obtained from the Federal

Office for Statistics [13]. The population with diabetes was estimated in the adult population based on age- (30–59, 60–69, 70–79, ≥80 years) and sex-specific diabetes prevalence from two German nationwide surveys (German Health Interview and Examination Surveys, GNHIES98 and DEGS1) [14–16] performed in 1997–1999 and 2008–2011, respectively. In both surveys, diabetes was defined by intake of glucose-lowering medication, by self-report of physician-diagnosed diabetes or by an HbA_{1c} value above 47.5 mmol/mol (6.5%) within the last week before the survey [17]. These two surveys are believed to be the only nationwide data sources with a comparable study design that allow the estimation of age- and sex-specific diabetes prevalence, including undetected diabetes, over more than a decade. Since both surveys were truncated at the age of 80 years, and given findings of previous studies [14], we assumed that diabetes prevalence remained constant among people above 80 years. For the main analysis we assumed that the estimated age- and sex-specific diabetes prevalence increased linearly from 2002 to 2011 and also continued to do so thereafter until 2016. Nevertheless, we repeated the main analysis with constant age- and sex-specific diabetes prevalence during the years 2011–2016 in the sensitivity analysis.

Assessment of people with incident RRT and data assessment In the present analysis, we examined all people aged at least 30 years at the time of first RRT between January 2002 and December 2016. According to our previous study [9], an incident RRT was defined as the first dialysis or primary kidney or combined pancreas-kidney transplantation due to chronic kidney disease. Individuals with RRT due to typical acute kidney insufficiency due to sepsis and other agents were excluded, as were individuals with transplant failure and individuals from outside of the study region.

Demographic data such as age and sex were available for all people with a first RRT. A person was classified as having diabetes according to a history of diabetes, use of a glucose-lowering agent or having $HbA_{1c} \geq 47.5$ mmol/mol (6.5%) at the start of RRT [18]. Likewise, the reason for RRT was determined according to established classifications [19–21]. Diabetic nephropathy as a reason for RRT was assumed when an individual had macroalbuminuria or microalbuminuria and diabetic retinopathy, both in the absence of another disease associated with ESRD [22]. Additionally, the type of RRT was documented (i.e. peritoneal dialysis or haemodialysis).

Furthermore, several clinical variables such as GFR (using the Modification of Diet in Renal Disease [MDRD] formula or the Chronic Kidney Disease Epidemiology Collaboration formula [CKD-Epi]), HbA_{1c} value, initial form of RRT, start of dialysis in the clinic (yes vs no), BMI, information regarding type of diabetes and diabetes duration were ascertained.

Moreover, information was obtained regarding the following comorbidities at the start of RRT: hypertension, CHD, congestive heart failure, myocardial infarction, peripheral artery occlusive disease, amputation, stroke, malignant tumour and presence of diabetic retinopathy among individuals with diabetes only.

Statistical analysis We performed analyses for the population as a whole and separately for men and women. We estimated the number of people with diabetes by multiplying the study population with the estimated diabetes prevalence in each stratum, defined by sex and age (30–59, 60–69, 70–79, ≥80 years). Person-years (PY) were calculated by taking the estimated number of people with and without diabetes for each calendar year. We computed stratum-specific and age- and sex-standardised incidence rates (IRs) of RRT with 95% CIs in the estimated population with and without diabetes for each calendar year, using the German population of 2009 as the standard population. Moreover, we estimated the IR ratio by comparing the population with and without diabetes from the standardised IRs. Furthermore, we computed attributable risk among the population with diabetes and population attributable risk due to diabetes along with 95% CIs in order to describe what proportion of RRT could theoretically be avoided if the exposure (i.e. diabetes) was omitted. Time trends were investigated by first fitting separate Poisson regression models with IR of RRT as the dependent variable for individuals with and without diabetes. Age and year of RRT as linear continuous difference from baseline year 2002 were used as the independent variables. The lowest age group (30–59 years) was used as a reference group. Moreover, we fitted analogous Poisson models for the entire population. The variable 'presence of diabetes' (yes vs no) and an interaction term for diabetes and years since 2002 were also included.

Furthermore, we estimated IRs and trends of RRT due only to diabetic nephropathy in the diabetic population.

In order to take over-dispersion of the outcome variable into account, all analyses were conducted with the de-scale adjustment based on cumulated data on the covariate strata. The analysis was computed using the statistical analysis system, SAS (SAS for Windows 7, Release 9.4 TS1M1, SAS Institute, Cary, NC, USA).

Ethics All participants were asked to provide their written, informed consent for participation when they started RRT. Individuals who declined (less than 1% of all participants) were excluded from the analysis. The study was approved by the local ethics committee.

Results

Study population The data covered the population aged at least 30 years in the study region (2002: 219,046, 2016: 213,120). Diabetes prevalence in this region increased among

men from 11.8% in 2002 to 13.7% in 2016 but remained nearly constant among women (2002: 11.4%, 2016: 11.4%).

There were 1107 people with a first RRT between 2002 and 2016. The baseline characteristics of these people regarding age, sex, clinical variables and comorbidities are shown in Table 1. The majority of the people starting RRT were men (61.2%). The age distribution of people with RRT was similar among people with and without diabetes, with a mean age of 71.6 years at the time of the first RRT. Nevertheless, the mean age increased significantly during the study period from 67.4 years in 2002 to 73.1 years in 2016 (p value linear regression: $p < 0.001$), with similar increases among all subgroups.

Almost half of all 1107 individuals were classified as having diabetes, with similar proportions among men and women.

The majority of individuals with diabetes had type 2 diabetes (95.6%) and the mean duration of diabetes at the time of the first RRT was 16.9 years, with similar numbers in both sexes. As expected, the mean HbA_{1c} value was significantly higher among people with diabetes than among those without diabetes (HbA_{1c}: 47.7 mmol/mol [6.5%] vs HbA_{1c}: 36.5 mmol/mol [5.5%], p value t test <0.001), with similar values in men and women.

In almost half of the people with diabetes, diabetic nephropathy was the reason for RRT (49.1%). Vascular nephropathy (kidney disease due to hypertension and micro- and macrovascular diseases) was the reason for RRT in about one-third (33.8%). In the population without diabetes, the most common reason for RRT was vascular nephropathy (39.8%). The majority of people who started RRT began with haemodialysis (61.5%) followed by peritoneal dialysis (38.5%), with similar numbers in all subgroups, while only one person underwent transplantation as the first RRT.

The majority of dialyses started in the clinic (78.6%), with similar proportions in all subgroups. The GFR value was significantly higher in men with diabetes than in those without (p value = 0.0012). In women, this difference was not significant (p value = 0.427).

People with diabetes had significantly more comorbidities and higher BMI at the time of first RRT than those without diabetes (p values χ^2 test and t test <0.05, respectively), with the exception of malignant tumour, where an inverse association was observed (p value < 0.001). The proportion of comorbidities was higher among men for all comorbidities except diabetic retinopathy.

IR, relative and attributable risk The age- and sex-standardised IRs of the first RRT are shown in Table 2 and Fig. 1. There were some fluctuations, which were particularly evident in the population with diabetes. During the observation period, the IR in the population with diabetes ranged from 56.2 per 100,000 PY (95% CI 31.1, 81.4) in 2008 to 140.5 per 100,000 PY (95% CI 80.6, 200.4) in 2016, without sex differences. This rate was substantially lower in the population without diabetes, with values between 17.2 (95% CI 11.0, 23.4) in 2002 and 29.5 (95% CI 21.5, 37.5) in 2009. The RR comparing the IRs among the populations with diabetes and without diabetes ranged between 2.5 (95% CI 1.4, 4.4) in 2009 and 6.0 (95% CI 3.3, 10.8) in 2004. In people with diabetes, 78% of the RRT incidence was attributable to diabetes. In the entire population, one-third of the RRT incidence was attributable to diabetes. The IR was twice as high among men compared with women in subpopulations both with and without diabetes.

IR relating only to diabetic nephropathy tended to decrease, with the highest value in 2003 (87.4; 95% CI 42.6, 132.1) and the lowest value in 2010 (32.1; 95% CI 9.7, 54.5), and was about twofold higher among men than among women (see electronic supplementary material [ESM] Table 1, ESM Fig. 1).

Analysis of time trend and other covariates The results of the incidence trend from the fully adjusted Poisson models are shown in Table 3. The RRs in the population stratified by diabetes status are presented in models 1a and 1b. During the observation period, no change in the IR was observed in the population with diabetes (RR per calendar year, 1.02; 95% CI 0.99, 1.04) for either sex. Likewise, the IR remained nearly constant in the population without diabetes (RR 1.01; 95% CI 0.99, 1.03) both in men and in women. The IR increased substantially with increasing age, with a particularly strong increase in the population without diabetes.

Taking the entire population in model 2, the IR in the population with diabetes was almost fourfold that of the population without diabetes (RR 3.57; 95% CI 3.09, 4.13), with a higher difference among men (RR 4.14; 95% CI 3.39, 5.06). This pattern was particularly strong in the younger population but also persisted in the oldest age group (RR diabetes vs no diabetes <60 years, 12.60; 95% CI 9.04, 17.55; 80+ years: 2.04; 95% CI 1.58, 2.62) (data not shown). The interaction diabetes × calendar year as considered in model 3 was nonsignificant, indicating that the RR between the subpopulations with and without diabetes remained constant in both sexes. Results from the sensitivity analysis assumed that diabetes prevalence remained constant after 2011, meaning that they were similar to those from the main analysis (ESM Tables 2, 3).

When RRT due only to diabetic nephropathy was counted, the IR of RRT significantly decreased in the male population with diabetes (RR per calendar year, 0.96; 95% CI 0.93, 0.997) but not in the female population (RR per calendar year, 0.97; 95% CI 0.93, 1.02) (ESM Table 4).

Discussion

Statement of principal findings This is one of the few studies analysing the incidence of RRT in the population with diabetes compared with the population without diabetes. This study also

Table 1 Description of all people with first RRT and the background population, district of Mettmann, 2002–2016

Characteristic	Total	Men	Women	Diabetes	No diabetes	Men		Women	
						Diabetes	No diabetes	Diabetes	No diabetes
All years combined									
Number of people with RRT	1107	677	430	539	568	326	351	213	217
Mean age[a] (years [SD])	71.6 (11.6)	70.9 (11.2)	72.6 (12.2)	71.6 (10.6)	71.6 (12.5)	70.3 (10.2)[b]	71.5 (12.1)	73.5 (11.0)[b]	71.7 (13.2)
Number of people with RRT									
30–59 years	156	99	57	63	93	46	53	17	40
60–69 years	241	159	82	132	109	91	68	41	41
70–79 years	425	271	154	222	203	132	139	90	64
80 years and older	285	148	137	122	163	57	91	65	72
Year RRT started: 2002									
Number of people with RRT	59	35	24	29	30	17	18	12	12
Mean age[a] (years [SD])	67.4 (11.5)	66.0 (10.4)	69.4 (12.9)	70.1 (9.8)	64.8 (12.5)	68.2 (9.7)	63.9 (10.9)	72.8 (9.6)	66.0 (15.2)
Population at risk	219,046	103,210	115,836	25,319	193,727	12,156	91,054	13,163	102,673
Year RRT started: 2003									
Number of people with RRT	74	46	28	37	37	23	23	14	14
Mean age[a] (years [SD])	70.0 (10.4)	70.7 (10.6)	68.9 (10.2)	67.8 (8.8)	72.2 (11.5)	66.6 (8.1)	74.7 (11.5)	69.8 (10)	68.0 (10.7)
Population at risk	218,491	103,007	115,484	25,348	193,143	12,262	90,745	13,086	102,398
Year RRT started: 2004									
Number of people with RRT	60	34	26	30	30	18	16	12	14
Mean age[a] (years [SD])	69.6 (9.5)	68.7 (8.8)	70.7 (10.3)	69.4 (10.6)	69.8 (8.4)	67.8 (9.1)	69.8 (8.7)	71.8 (12.5)	69.7 >(8.3)
Population at risk	218,151	102,808	115,343	25,479	192,672	12,368	90,440	13,111	102,232
Year RRT started: 2005									
Number of people with RRT	73	43	30	37	36	22	21	15	15
Mean age[a] (years [SD])	69.9 (11.6)	69.6 (11.7)	70.2 (11.7)	68.9 (11.0)	70.9 (12.2)	68.1 (10.5)	71.2 (12.8)	70.0 (12.1)	70.4 (11.7)
Population at risk	217,947	102,815	115,132	25,508	192,439	12,436	90,379	13,072	102,060
Year RRT started: 2006									
Number of people with RRT	67	35	32	35	32	20	15	15	17
Mean age[a] (years [SD])	71.2 (11.2)	70.9 (9.3)	71.6 (13.1)	70.6 (8.8)	71.9 (13.4)	68.8 (8.0)	73.7 (10.3)	73.0 (9.4)	70.3 (15.9)
Population at risk	217,632	102,634	114,998	25,592	192,040	12,535	90,099	13,057	101,941
Year RRT started: 2007									
Number of people with RRT	68	38	30	32	36	17	21	15	15
Mean age[a] (years [SD])	72.7 (11.5)	73.0 (8.6)	72.2 (14.5)	74.1 (8.3)	71.4 (13.7)	71.0 (8.3)	74.6 (8.6)	77.6 (7.0)	66.9 (18.1)
Population at risk	217,160	102,339	114,821	25,709	191,451	12,644	89,695	13,065	101,756
Year RRT started: 2008									
Number of people with RRT	58	39	19	28	30	20	19	8	11
Mean age[a] (years [SD])	71.8 (10.4)	74.1 (8.0)	67.1 (13.2)	73.5 (7.0)	70.2 (12.7)	73.3 (7.9)	74.9 (8.2)	74.1 (4.6)	62.0 (15.2)
Population at risk	216,063	101,818	114,245	25,839	190,224	12,777	89,041	13,062	101,183
Year RRT started: 2009									
Number of people with RRT	80	49	31	28	52	15	34	13	18
Mean age[a] (years [SD])	71.6 (12.5)	69.6 (12.7)	74.7 (11.6)	73.0 (8.9)	70.8 (14.1)	71.3 (9.4)	68.8 (14.0)	74.9 (8.1)	74.6 (13.9)
Population at risk	215,345	101,391	113,954	26,065	189,280	12,950	88,441	13,115	100,839
Year RRT started: 2010									
Number of people with RRT	69	40	29	34	35	20	20	14	15
Mean age[a] (years [SD])	74.1 (9.8)	73.4 (9.6)	75.1 (10.2)	74.9 (9.4)	73.4 (10.3)	73.4 (10.3)	73.5 (9.1)	77.0 (7.7)	73.4 (12.1)
Population at risk	215,392	101,408	113,984	26,351	189,041	13,150	88,258	13,201	100,783
Year RRT started: 2011									
Number of people with RRT	74	44	30	43	31	26	18	17	13
Mean age[a] (years [SD])	73.2 (9.7)	71.3 (9.4)	75.9 (9.7)	72.9 (9.2)	73.6 (10.4)	70.7 (9.0)	72.3 (10.1)	76.3 (8.8)	75.5 (11.1)
Population at risk	211,020	99,046	111,974	25,908	185,112	12,930	86,116	12,978	98,996
Year RRT started: 2012									
Number of people with RRT	87	53	34	46	41	28	25	18	16
Mean age[a] (years [SD])	71.6 (13.1)	68.8 (13.8)	76.0 (11.8)	71.3 (12.2)	71.9 (14.3)	68.4 (12.3)	69.2 (14.5)	75.8 (10.8)	76.1 (13.3)
Population at risk	211,171	99,136	112,035	26,049	185,122	13,083	86,053	12,966	99,069
Year RRT started: 2013									
Number of people with RRT	77	48	29	37	40	22	26	15	14
Mean age[a] (years [SD])	68.9 (13.1)	67.8 (13.1)	73.2 (12.5)	69.0 (12.4)	70.6 (13.8)	68.2 (12.5)	67.4 (13.8)	70.2 (12.5)	76.4 (12.1)
Population at risk	211,319	99,259	112,060	26,128	185,191	13,217	86,042	12,911	99,149
Year RRT started: 2014									
Number of people with RRT	75	48	27	33	42	19	29	14	13
Mean age[a] (years [SD])	72.0 (12.4)	71.9 (12.0)	72.2 (13.2)	72.8 (12.3)	71.4 (12.6)	73.2 (11.1)	71.1 (12.7)	72.2 (14.2)	72.2 (12.7)
Population at risk	211,555	99,405	112,150	26,280	185,275	13,383	86,022	12,897	99,253
Year RRT started: 2015									
Number of people with RRT	90	66	24	41	49	27	39	14	10
Mean age[a] (years [SD])	73.9 (10.5)	74.3 (10.3)	72.5 (11.1)	71.9 (11.0)	75.5 (9.9)	72.4 (10.3)	75.7 (10.3)	70.9 (12.5)	74.9 (8.9)
Population at risk	212,393	99,968	112,425	26,324	186,069	13,517	86,451	12,807	99,618
Year RRT started: 2016									
Number of people with RRT	96	59	37	49	47	32	27	17	20
Mean age[a] (years [SD])	73.1 (13.7)	71.7 (13.5)	75.3 (13.9)	73.3 (13.5)	72.8 (14.0)	72.3 (11.8)	71.0 (15.4)	75.3 (16.4)	75.4 (11.9)
Population at risk	213,120	100,269	112,851	26,622	186,498	13,746	86,523	12,876	99,975
Diabetes duration (years [SD]) (138 missing)	–	–	–	16.9 (11.3)	–	16.9 (11.1)	–	16.9 (11.8)	–
Diabetes type (%) (24 missing)									
Type 1	–	–	–	4.4	–	3.9	–	5	–
Type 2	–	–	–	95.6	–	96.1	–	95.0	–

Table 1 (continued)

Characteristic	Total	Men	Women	Diabetes	No diabetes	Men		Women	
						Diabetes	No diabetes	Diabetes	No diabetes
HbA_{1c} value (mmol/mol [SD])[a] (295 missing)	42.4 (11.1)	42.3 (10.4)	42.7 (12.2)	47.7 (11.5)[b]	36.5 (7.0)[b]	47.4 (11.0)[b]	36.9 (6.2)[b]	48.2 (12.1)[b]	35.8 (8.1)[b]
HbA_{1c} value (% [SD])[a] (295 missing)	6.0 (1.0)	6.0 (1.0)	6.1 (1.1)	6.5 (1.0)[b]	5.5 (0.6)[b]	6.5 (1.0)[b]	5.5 (0.6)[b]	6.6 (1.1)[b]	5.4 (0.7)[b]
BMI (kg/m^2 [SD])[a] (202 missing)	27.7 (6.2)	27.7 (6.4)	27.7 (6.0)	29.4 (6.0)[b]	26.2 (6.0)[b]	29.6 (5.9)[b]	26.1 (6.3)[b]	29.1 (6.2)[b]	26.4 (5.5)[b]
Reason for RRT (%) (95 missing)									
Diabetic nephropathy	25.0	24.6	25.6	49.1	0	49.2	0	49.1	0
Vascular nephropathy	36.8	38.3	34.2	33.8	39.8	35.1	41.5	31.7	37.0
Glomerulonephropathy	12.2	10.9	14.3	5.2	19.3	4.4	17.3	6.4	22.8
Other/unknown	26.1	26.2	25.9	11.8	40.9	11.2	41.3	12.9	40.2
Initial treatment (%) (36 missing)									
Transplantation	0.1	0.2	0	0.2	0	0.3	0	0	0
HD	61.5	61.4	61.4	61.6	61.3	61.9	61.3	61.1	61.7
Shunt	36.0	38.5	31.9	37.5	34.5	40.3	36.9	33.2	30.6
Central venous catheter	25.5	22.9	29.5	24.1	26.8	21.6	24.2	27.9	31.1
PD	38.5	38.4	38.6	38.2	38.7	37.8	38.9	38.9	38.3
Start of dialysis in the clinic (%) (82 missing)	78.6	77.9	79.9	79.3	78.0	78.8	77.0	80.1	79.6
GFR value (MDRD: ml/min [SD])[a, c] (158 missing)	15.8 (10.9)	16.4 (10.1)	14.9 (11.9)	17.0 (9.2)[b]	14.7 (12.2)[b]	18.1 (9.8)[b]	14.9 (10.1)[b]	15.4 (8.1)	14.3 (14.8)
GFR value (CKD-Epi: ml min^{-1} 1.73 m^{-2} [SD])[a, d] (15 missing)	15.4 (13.8)	17.3 (15.8)	11.5 (6.9)	16.6 (14.2)	14.3 (13.3)	19.0 (16.6)	15.9 (15.1)	12.3 (6.4)	10.8 (7.4)
Congestive heart failure (%)[a] (46 missing)	22.6	24.4	19.9	28.4[b]	17.0[b]	29.0	19.9	27.5	12.2
Diabetic retinopathy (%)[a] (45 missing)	15.2	14.0	17.0	30.7	0.0	28.7	0.0	33.8	0.0
Hypertension (%)[a] (41 missing)	89.6	90.0	88.9	93.7[b]	85.5[b]	93.1[b]	87.1[b]	83.1[b]	94.7[b]
CHD (%)[a] (32 missing)	38.1	44.1	28.5	46.5[b]	29.9[b]	50.8[b]	37.9[b]	40.0[b]	16.8[b]
Myocardial infarction (%)[a] (41 missing)	15.6	18.1	11.6	19.4[b]	11.9[b]	20.7	15.7	17.3[b]	5.8[b]
Peripheral artery occlusive disease (%)[a] (31 missing)	21.8	25.5	15.8	28.3[b]	15.4[b]	33.4[b]	18.1[b]	20.5[b]	11.1[b]
Minor amputation (%)[a] (41 missing)	2.5	3.2	1.5	3.6[b]	1.5[b]	4.7[b]	1.8[b]	1.9	1.0
Major amputation (%)[a] (41 missing)	2.6	3.4	1.5	4.0[b]	1.3[b]	5.6[b]	1.2[b]	1.4	1.4
Stroke (%)[a] (32 missing)	16.9	18.1	15.1	19.9[b]	14.1[b]	21.0	15.4	18.1	12.0
Malignant tumour (%)[a] (31 missing)	24.3	26.3	21.0	19.5[b]	28.9[b]	20.1[b]	32.3[b]	18.6	23.4

[a] Measured during start of RRT

[b] Significant differences between people with diabetes and without diabetes (p value<0.05 unpaired t test for continuous variables, χ^2 test for categorical variables)

[c] Before 31 December 2013

[d] After 1 January 2014

CKD-Epi, Chronic Kidney Disease Epidemiology Collaboration formula; HD, haemodialysis; MDRD, Modification of Diet in Renal Disease formula; PD, peritoneal dialysis

evaluated the trend of the incidence of RRT over a time period of 15 years. As expected, the IRs were substantially higher among people with diabetes, with an almost fourfold-increased IR. Men had twice as high a risk of RRT compared with women. The IRs in subpopulations both with and without diabetes and, thus, the corresponding RRs, mainly remained constant throughout the study period, with consistent results in both sexes.

Discussion of important differences in results A comparison with other studies is very difficult. We found only a few population-based studies analysing age- and sex-standardised IRs among people with and without diabetes. Furthermore, most of the studies investigating the IR of RRT in the population with diabetes only considered diabetic nephropathy as a primary reason for RRT, and not diabetes as a comorbidity.

The IRs among people with diabetes in the current study were somewhat lower than in the previous study in the same study region [9], which included the years 2002–2008: IR 97.9 (95% CI 86.7, 109.1) vs 167 (95% CI 125, 208) per 100,000 PY. This discrepancy is mainly the result of a different methodological approach regarding the estimation of the diabetic population as a population at risk. In the previous study, diabetes prevalence was estimated using the former

Table 2 Incidence of RRT, district of Mettmann, 2002–2016

Variable	IRs[a] (95% CI) per 100,000 PY			Relative and attributable risks (95% CI)		
	IRt	IRd	IRn	RR	ARE	PAR
All years combined						
Total population	32.8 (30.9, 34.7)	97.9 (86.7, 109.1)	21.8 (20.0, 23.6)	4.5 (3.9, 5.2)	0.78 (0.74, 0.81)	0.34 (0.27, 0.40)
Men	46.9 (43.4, 50.5)	129.5 (111.2, 147.7)	32.9 (29.4, 36.4)	3.9 (3.3, 4.7)	0.75 (0.70, 0.79)	0.30 (0.20, 0.39)
Women	22.3 (20.2, 24.5)	69.9 (56.6, 83.2)	14.1 (12.2, 16.0)	5.0 (3.9, 6.3)	0.80 (0.75, 0.84)	0.37 (0.26, 0.46)
Stratified by year						
2002	28.4 (21.1, 35.8)	93.6 (50.4, 136.7)	17.3 (10.9, 23.6)	5.4 (3.0, 9.8)	0.82 (0.67, 0.90)	0.39 (0.35, 0.43)
2003	36.6 (28.1, 45.1)	109.8 (63.1, 156.5)	25.4 (17.0, 33.7)	4.3 (2.5, 7.4)	0.77 (0.60, 0.87)	0.31 (0.14, 0.44)
2004	27.5 (20.5, 34.6)	103.0 (54.5, 151.5)	17.3 (11.0, 23.6)	6.0 (3.3, 10.8)	0.83 (0.69, 0.91)	0.37 (0.05, 0.58)
2005	33.8 (26.0, 41.6)	109.1 (62.4, 155.9)	21.5 (14.3, 28.6)	5.1 (3.0, 8.7)	0.80 (0.66, 0.89)	0.36 (0.22, 0.48)
2006	30.9 (23.4, 38.3)	97.9 (55.9, 139.9)	19.4 (12.6, 26.2)	5.0 (2.9, 8.8)	0.80 (0.65, 0.89)	0.37 (0.12, 0.55)
2007	31.1 (23.7, 38.5)	67.0 (40.2, 93.9)	21.5 (14.4, 28.5)	3.1 (1.9, 5.2)	0.68 (0.46, 0.81)	0.31 (0.15, 0.44)
2008	25.9 (19.2, 32.5)	56.2 (31.1, 81.4)	17.2 (11.0, 23.4)	3.3 (1.8, 5.8)	0.69 (0.46, 0.83)	0.33 (0.02, 0.55)
2009	35.1 (27.4, 42.8)	72.8 (36.6, 109.0)	29.5 (21.5, 37.5)	2.5 (1.4, 4.4)	0.60 (0.29, 0.77)	0.16 (0.00, 0.30)
2010	29.1 (22.2, 36.0)	81.0 (43.8, 118.3)	19.2 (12.8, 25.5)	4.2 (2.4, 7.5)	0.76 (0.58, 0.87)	0.34 (0.07, 0.53)
2011	31.9 (24.6, 39.2)	100.6 (59.7, 141.5)	17.6 (11.4, 23.7)	5.7 (3.3, 9.8)	0.83 (0.70, 0.90)	0.45 (0.24, 0.60)
2012	37.7 (29.7, 45.6)	129.2 (76.3, 182.0)	22.6 (15.7, 29.6)	5.7 (3.4, 9.5)	0.82 (0.71, 0.89)	0.40 (0.25, 0.52)
2013	33.4 (25.9, 40.9)	119.0 (65.8, 172.3)	22.2 (15.3, 29.1)	5.4 (3.1, 9.3)	0.81 (0.68, 0.89)	0.34 (0.14, 0.49)
2014	31.4 (24.2, 38.6)	74.4 (39.3, 109.6)	22.9 (16.0, 29.9)	3.2 (1.9, 5.7)	0.69 (0.46, 0.82)	0.27 (0.04, 0.45)
2015	37.0 (29.3, 44.7)	118.1 (67.2, 169.1)	26.5 (19.1, 34.0)	4.5 (2.7, 7.4)	0.78 (0.62, 0.87)	0.28 (0.12, 0.41)
2016	39.0 (31.1, 46.9)	140.5 (80.6, 200.4)	24.6 (17.5, 31.7)	5.7 (3.4, 9.6)	0.82 (0.71, 0.90)	0.37 (0.23, 0.49)
Men						
2002	37.8 (24.7, 50.9)	131.0 (57.9, 204.1)	22.4 (11.7, 33.2)	5.8 (2.8, 12.2)	0.83 (0.64, 0.92)	0.41 (0.28, 0.51)
2003	56.6 (39.2, 74.0)	134.4 (67.1, 201.8)	44.1 (25.1, 63.1)	3.0 (1.6, 5.9)	0.67 (0.36, 0.83)	0.22 (0.08, 0.34)
2004	35.2 (22.9, 47.5)	130.0 (56.5, 203.5)	20.9 (10.4, 31.4)	6.2 (2.9, 13.3)	0.84 (0.66, 0.92)	0.41 (0.00, 0.70)
2005	46.8 (32.0, 61.5)	133.7 (65.0, 202.5)	31.2 (16.9, 45.5)	4.3 (2.2, 8.5)	0.77 (0.54, 0.88)	0.33 (0.15, 0.48)
2006	38.4 (25.2, 51.6)	122.5 (55.3, 189.7)	23.7 (11.1, 36.3)	5.2 (2.4, 11.1)	0.81 (0.58, 0.91)	0.38 (0.00, 0.65)
2007	40.5 (27.3, 53.8)	83.5 (36.3, 130.6)	31.6 (17.7, 45.5)	2.6 (1.3, 5.4)	0.62 (0.22, 0.81)	0.22 (0.04, 0.37)
2008	41.8 (28.4, 55.3)	94.1 (44.8, 143.3)	28.3 (15.2, 41.4)	3.3 (1.7, 6.7)	0.70 (0.39, 0.85)	0.32 (0.00, 0.54)
2009	50.3 (36.1, 64.5)	100.4 (33.3, 167.5)	45.6 (29.9, 61.2)	2.2 (1.0, 4.7)	0.55 (0.04, 0.79)	0.09 (0.00, 0.32)
2010	41.2 (28.4, 54.1)	123.0 (52.3, 193.7)	27.5 (15.3, 39.7)	4.5 (2.2, 9.3)	0.78 (0.54, 0.89)	0.33 (0.00, 0.55)
2011	43.4 (30.5, 56.3)	130.3 (65.2, 195.4)	23.8 (12.7, 35.0)	5.5 (2.8, 10.8)	0.82 (0.64, 0.91)	0.45 (0.15, 0.65)
2012	53.2 (38.8, 67.7)	183.9 (91.2, 276.5)	33.1 (20.0, 46.3)	5.5 (2.9, 10.5)	0.82 (0.66, 0.91)	0.38 (0.20, 0.51)
2013	46.3 (33.1, 59.4)	146.8 (63.0, 230.6)	32.7 (20.1, 45.4)	4.5 (2.2, 8.9)	0.78 (0.56, 0.89)	0.29 (0.01, 0.49)
2014	46.2 (33.1, 59.4)	79.6 (31.2, 127.9)	38.1 (24.1, 52.1)	2.1 (1.0, 4.2)	0.52 (0.03, 0.76)	0.18 (0.00, 0.38)
2015	63.7 (48.3, 79.1)	143.8 (67.2, 220.4)	52.3 (35.8, 68.8)	2.7 (1.5, 5.1)	0.64 (0.32, 0.80)	0.18 (0.14, 0.22)
2016	56.3 (41.9, 70.6)	206.2 (102.5, 309.9)	34.3 (21.3, 47.4)	6.0 (3.2, 11.3)	0.83 (0.69, 0.91)	0.39 (0.22, 0.52)
Women						
2002	20.1 (12.0, 28.2)	60.5 (11.3, 109.6)	12.2 (5.2, 19.2)	5.0 (1.8, 13.4)	0.8 (0.46, 0.93)	0.39 (0.19, 0.55)
2003	24.2 (15.1, 33.2)	89.1 (22.7, 155.6)	15.3 (7.1, 23.4)	5.8 (2.3, 14.6)	0.83 (0.57, 0.93)	0.37 (0.00, 0.61)
2004	20.8 (12.7, 28.9)	79.1 (14.1, 144.0)	13.9 (6.5, 21.3)	5.7 (2.1, 15.1)	0.82 (0.53, 0.93)	0.33 (0.00, 0.66)
2005	24.9 (16.0, 33.9)	89.9 (24.3, 155.4)	15.4 (7.5, 23.3)	5.8 (2.4, 14.2)	0.83 (0.58, 0.93)	0.38 (0.15, 0.55)
2006	25.6 (16.7, 34.6)	74.8 (23.6, 125.9)	17.6 (9.2, 26.0)	4.3 (1.8, 9.8)	0.77 (0.46, 0.90)	0.31 (0.04, 0.51)
2007	23.6 (15.1, 32.1)	48.7 (23.3, 74.1)	14.5 (7.2, 21.9)	3.4 (1.6, 6.9)	0.70 (0.38, 0.86)	0.38 (0.15, 0.55)
2008	15.7 (8.6, 22.8)	26.6 (7.6, 45.6)	10.9 (4.5, 17.4)	2.4 (1.0, 6.2)	0.59 (0.00, 0.84)	0.30 (0.00, 0.59)
2009	23.5 (15.2, 31.9)	46.8 (19.9, 73.7)	17.4 (9.3, 25.5)	2.7 (1.3, 5.6)	0.63 (0.22, 0.82)	0.26 (0.12, 0.38)
2010	21.6 (13.7, 29.5)	45.7 (20.1, 71.3)	14.2 (7.0, 21.4)	3.2 (1.5, 6.9)	0.69 (0.34, 0.85)	0.34 (0.00, 0.61)

Table 2 (continued)

Variable	IRs[a] (95% CI) per 100,000 PY			Relative and attributable risks (95% CI)		
	IRt	IRd	IRn	RR	ARE	PAR
2011	21.9 (14.0, 29.8)	73.5 (23.4, 123.7)	11.9 (5.4, 18.4)	6.2 (2.6, 14.8)	0.84 (0.61, 0.93)	0.45 (0.01, 0.70)
2012	24.8 (16.4, 33.3)	76.1 (25.8, 126.3)	14.7 (7.5, 21.9)	5.2 (2.3, 11.8)	0.81 (0.56, 0.92)	0.41 (0.07, 0.62)
2013	22.0 (13.9, 30.1)	91.8 (26.4, 157.2)	13.1 (6.2, 19.9)	7.0 (2.9, 17.1)	0.86 (0.66, 0.94)	0.41 (0.00, 0.66)
2014	20.5 (12.6, 28.3)	71.1 (20.0, 122.3)	12.2 (5.5, 18.9)	5.8 (2.4, 14.4)	0.83 (0.58, 0.93)	0.40 (0.00, 0.68)
2015	18.2 (10.8, 25.5)	98.3 (30.7, 165.8)	9.0 (3.4, 14.7)	10.9 (4.3, 27.6)	0.91 (0.77, 0.96)	0.50 (0.00, 0.78)
2016	26.0 (17.4, 34.6)	79.8 (20.3, 139.4)	17.9 (9.9, 25.8)	4.5 (1.9, 10.6)	0.78 (0.47, 0.91)	0.31 (0.01, 0.52)

[a] Standardised to the German population, 2009

IRt, all cases of RRT in total population; IRd, cases of RRT in individuals with diabetes in population with diabetes; IRn, cases of RRT in individuals without diabetes in population without diabetes; RR relative risk (IRd/IRn); ARE, attributable risk of RRT due to diabetes among the population with diabetes ([IRd – IRn]/IRd); PAR, attributable risk of RRT due to diabetes in total population ([IRt – IRn]/ IRt)

East German diabetes registry, the data of which are from the late 1980s when prevalence was quite low [23]. In contrast, diabetes prevalence was estimated in the current study using more recent data from nationwide German surveys with a substantially higher diabetes prevalence, partly due to the inclusion of undetected diabetes cases [14, 17]. However, the IRs among people without diabetes were comparable between the two studies (21.8 [95% CI 20.0, 23.6] in the present study vs 20 [95% CI 18, 23] in the previous study). Therefore, when comparing the incidence of RRT among people with and without diabetes, relative risk was considerably lower in the current study (almost fourfold) than in the previous study (almost eightfold).

An international comparison revealed one population-based study from Canada conducted in 1999–2000 with a comparable study design. The age- and sex-adjusted IR in the population with diabetes in that study was 132.9 per 100,000 PY and thus in line with our findings. In contrast, the IR among people without diabetes in the Canadian study was 11.0 and therefore much lower than our results, with a resulting higher corresponding RR of 12 [3].

Although some other studies also analysed the IR of RRT among people with diabetes and took into account diabetes as a comorbidity, they represented only the crude IRs [10, 11] or crude RRs [2], and were therefore not wholly comparable with our results.

Due to the fact that renal registers usually record only the primary cause for RRT, the epidemiological studies based on these data sources are only able to estimate the incidence of RRT that was due to diabetic nephropathy [5, 24–28]. Moreover, most of these studies reported IRs of diabetic nephropathy by using the total population as a denominator and not the population with diabetes at risk [5, 24, 26, 28]. This approach has limitations since it does not consider the prevalence of diabetes in the background population. These studies are therefore not comparable with the current study. Only one study from the USA [25] reported age-standardised IRs of diabetic nephropathy including estimation of the population with diabetes at risk: the IR varied between 260.2 per 100,000 PY in 2000 and 173.9 in 2014 [25]. A study from Catalonia, Spain, reported that the crude IR changed from 48.95 per 100,000 PY in 1994 to 59.36 in 2010 [27].

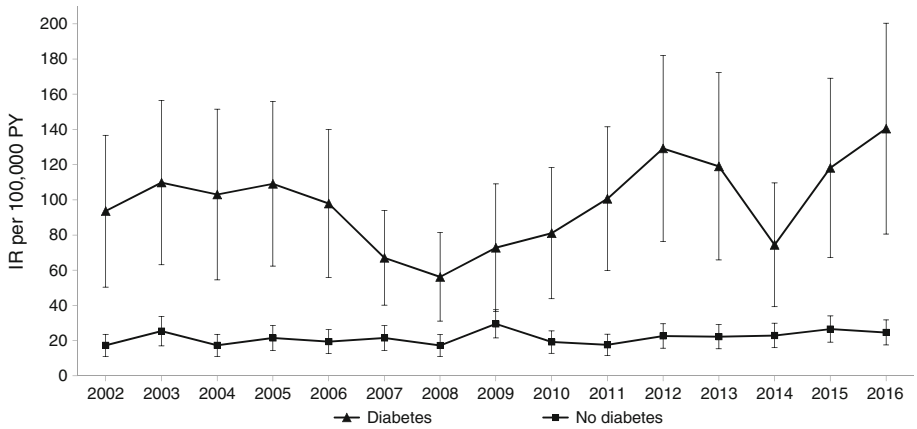

Fig. 1 Time trend of age- and sex-standardised IRs of first RRT (including 95% CI) in men and women with and without diabetes

Table 3 Results of Poisson models: RRs for RRT, district of Mettmann, 2002–2016

Variable	RR for RRT (95% CI)		
	Both sexes	Men	Women
Model 1a (population with diabetes)			
Calendar year	1.02 (0.99, 1.04)	1.01 (0.99, 1.03)	1.01 (0.99, 1.04)
Men vs women	2.29 (1.89, 2.78) *	–	–
Age (years) [a]			
≥80	19.88 (14.90, 26.53) *	2.70 (1.93, 3.78) *	3.89 (2.43, 6.23) *
70–79	12.00 (9.10, 15.81) *	2.46 (1.84, 3.28) *	3.55 (2.25, 5.61) *
60–69	4.63 (3.39, 6.32) *	1.77 (1.31, 2.41) *	2.52 (1.53, 4.15) *
Model 1b (population without diabetes)			
Calendar year	1.01 (0.99, 1.03)	1.03 (0.999, 1.06)	0.99 (0.96, 1.03)
Men vs women	1.67 (1.43, 1.94) *	–	–
Age (years) [a]			
≥80	3.04 (2.33, 3.96) *	25.52 (17.13, 38.02) *	13.41 (9.05, 19.86) *
70–79	2.76 (2.16, 3.51) *	15.25 (10.52, 22.12) *	7.86 (5.26, 11.74) *
60–69	1.97 (1.52, 2.55) *	5.33 (3.50, 8.13) *	3.67 (2.36, 5.70) *
Model 2 (entire population)			
Calendar year	1.01 (0.995, 1.03)	1.02 (0.99, 1.04)	1.00 (0.98, 1.03)
Diabetes (yes vs no)	3.57 (3.09, 4.13) *	3.25 (2.64, 4.01) *	4.14 (3.39, 5.06) *
Men vs women	1.98 (1.72, 2.29) *		
Age (years) [a]			
≥80	10.40 (8.19, 13.22) *	11.55 (8.13, 16.41) *	8.80 (6.36, 12.16) *
70–79	7.60 (6.07, 9.52) *	8.30 (6.03, 11.41) *	6.52 (4.74, 8.97) *
60–69	4.00 (3.14, 5.09) *	4.24 (3.01, 5.96) *	3.67 (2.60, 5.19) *
Model 3 (entire population – including interaction term)			
Calendar year	1.02 (0.997, 1.04)	1.03 (1.002, 1.07)	1.00 (0.97, 1.03)
Diabetes (yes vs no)	3.95 (3.04, 5.14) *	4.30 (2.84, 6.51) *	3.72 (2.55, 5.43) *
Men vs women	2.00 (1.72, 2.27) *	–	–
Age (years) [a]			
≥80	10.4 (8.20, 13.25) *	11.57 (8.19, 16.46) *	8.81 (6.40, 12.28) *
70–79	7.60 (6.09, 9.55) *	8.30 (6.08, 11.47) *	6.53 (4.77, 9.06) *
60–69	3.99 (3.14, 5.09) *	4.21 (3.01, 5.94) *	3.68 (2.61, 5.23) *
Diabetes × calendar year	0.98 (0.95, 1.02)	0.96 (0.92, 1.01)	1.01 (0.97, 1.06)

[a] Baseline: <60 years

*$p < 0.05$

The incidence of RRT considering only diabetic nephropathy in the current study was largely comparable to the study results from Catalonia, Spain [27], but approximately five times lower than the study from the USA [25].

We did not find any significant time trend regarding IRs or RRs during the study period 2002–2016.

Our results are in line with a study from Italy, which analysed the incidence of dialysis during the years 2004–2013 in the populations with and without diabetes and did not observe a significant change [2]. In contrast, a study from Hong Kong reported a significant decrease in the incidence of ESRD (4% per year in the fully adjusted model) among individuals with type 2 diabetes during the years 2000–2012 [11].

The studies that only counted diabetic nephropathy as a reason for RRT reported a decrease of RRT incidence. A study from the USA reported a reduction of about a third between 2000 and 2014 [25] and the study from Catalonia, Spain, reported a slight decrease since 2002 [27]. In our study we observed a significant decrease among men but not among women with diabetes (ESM Table 4).

Strengths and weaknesses of the study Several limitations have to be considered. First, we analysed the data from one regional dialysis centre in Germany that covered a population of about 310,000 inhabitants. Therefore, only a restricted generalisation of the data to the whole German population

was possible. However, the results of RRT incidence with respect to the whole population of the study region in 2006 were justifiably comparable to national German data: 254 per million population vs 213 per million population [20]. Second, the diabetic population as a population at risk was estimated using data from two nationwide German surveys performed in 1997–1999 and 2008–2011. Although regional differences are reported in diabetes prevalence in Germany, a recent analysis based on nationwide claims data revealed that the prevalence of diabetes in the study region was highly comparable to national diabetes prevalence [29]. Third, diabetes prevalence could only be estimated up until 2011, and thus for the main analysis we assumed that diabetes prevalence increased linearly as of 2011. Nevertheless, we also performed a sensitivity analysis using constant diabetes prevalence for the years 2011–2016 with no effect on the main results. Finally, we cannot rule out that some people from the study region started RRT outside of the study region, which would lead to an underestimation. However, individuals with ESRD receive dialysis at least once a week over a long time period. Most therefore prefer to travel only a short distance within the study region. We therefore assume that the collection of RRT cases in the study region is largely complete.

A main strength of our study was that we estimated the incidence of RRT in people with diabetes compared with people without diabetes independently of the underlying reason for RRT. The majority of studies published were able to identify only people with diabetes in whom diabetic nephropathy was the main reason for RRT. This methodological approach could lead to an underestimation of people with diabetes, since diabetic nephropathy was only reported as primary renal disease in approximately half of the individuals with type 2 diabetes [30]. An additional problem is that although diagnosis of diabetic nephropathy is based on established guidelines [22], in practice it is not always easy (especially among individuals with type 2 diabetes) to differentiate between diabetic nephropathy as a main reason for ESRD and diabetes as a comorbidity when other diseases in individuals with diabetes co-exist, e.g. hypertension or renal disease with nondiabetic pathogenesis [30, 31]. A biopsy could clarify the diagnosis of diabetic nephropathy but is usually only performed among a small group of individuals [30, 31]. All of these factors could lead to an over- or underestimation of diabetic nephropathy as a reason for ESRD. A further strength of our study was the population-based design. We conducted our study using valid data from one well-documented regional dialysis centre. We were therefore able to report clinical data relating to diabetes type and diabetes duration as well as comorbidities upon commencement of RRT. Finally, we estimated the IR over a long study period which allowed us to evaluate a time trend of 15 years.

Unanswered questions and future research The IR of RRT remained substantially higher among people with diabetes, with an almost fourfold-increased RR. Men have a twofold-increased risk of RRT compared with women. The IRs among the subpopulations with and without diabetes and the RRs during the study period largely remained mainly constant, with consistent results in both sexes. However, the considered study region was fairly small. Therefore, future research in a nationwide population is needed to confirm these findings.

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Data availability The data that support the findings of this study are available from the authors upon reasonable request and with permission of the dialysis centre of Mettmann.

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Contribution statement AI and MK designed the study and co-drafted the first version of the article. MK collected and provided data. TK, TW, LCR and MN contributed to the overall coordination, data collection and research data. HC and MN analysed and interpreted the findings and drafted the first version of the article. All authors interpreted the analysis, and reviewed and provided input into the final manuscript and gave their final approval of the version to be published. AI is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Renal Replacement Therapy in People With and Without Diabetes in Germany, 2010–2016: An Analysis of More Than 25 Million Inhabitants

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OBJECTIVE

Epidemiological studies have shown contradictory results regarding the time trend of end-stage renal disease (ESRD) in people with diabetes. This study aims to analyze the incidence of ESRD, defined as chronic renal replacement therapy (RRT), to investigate time trends among people with and without diabetes in Germany and to examine whether these patterns differ by age and sex.

RESEARCH DESIGN AND METHODS

The data were sourced from nationwide data pooled from two German branches of statutory health insurances covering ∼25 million inhabitants. We estimated age- and sex-standardized incidence rates (IRs) for chronic RRT among people with and without diabetes in 2010–2016 and the corresponding relative risks. Time trends were analyzed using Poisson regression.

RESULTS

We identified 73,638 people with a first chronic RRT (male 60.0%, diabetes 60.6%, mean age 71.3 years). The IR of chronic RRT among people with diabetes (114.1 per 100,000 person-years [95% CI 110.0–117.2]) was almost six times higher than among people without diabetes (19.6 [19.4–19.8]). A consistent decline in IR was observed among people with diabetes (3% annual reduction, $P < 0.0001$) for both sexes and all age classes. In contrast, no consistent change of IR was identified in people without diabetes. Only among women aged <40 years ($P = 0.0003$) and people aged ≥80 years ($P < 0.0001$) did this IR decrease significantly.

CONCLUSIONS

Incidence of chronic RRT remained significantly higher among people with diabetes. The IR decreased significantly in people with diabetes independent of age and sex. Time trends were inconsistent in people without diabetes.

End-stage renal disease (ESRD) is a life-threatening complication in patients with diabetes, resulting in reduced quality of life, high mortality, and increased medical costs (1–5). A number of epidemiological studies estimated that one-half of

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patients with ESRD have diabetes when starting chronic renal replacement therapy (RRT) (6–8). Nevertheless, data comparing the RRT incidence in people with diabetes with those without diabetes are limited (9) and show wide variation, with incidence rates (IRs) among people with diabetes ranging from 59 per 100,000 person-years (PY) (10) to 678 per 100,000 PY (11). The relative risk (RR) comparing IRs in people with and without diabetes ranged from 4 (12) to 8 (11). However, different methodological approaches among the studies reduce the comparability of results. In particular, a high number of studies referred the RRT incidence in people with diabetes to the entire population (6,13–15). Other studies solely analyzed diabetes-associated ESRD with diabetic nephropathy as the primary reason for RRT, which is the cause of ESRD in only one-half of people with type 2 diabetes (7,10). The results of those population-based studies, which analyzed the time trend of RRT IRs among people with diabetes irrespective of the underlying reason for RRT in the diabetic population, were contradictory. A decrease in incidence was seen in Hong Kong (16), whereas a stable time trend was found in Italy (17) and, indeed, an increasing trend found in Australia when solely considering type 2 diabetes (18). Moreover, some studies reported significant age differences regarding the time trend of RRT incidence (18,19). A U.S. study observed an increased incidence of ESRD as a result of diabetic nephropathy among people aged 18–45 years since 2010 but a plateaued trend among people aged ≥45 years (19). These results demonstrate the relevance of age- and sex-specific analysis for a correct understanding and interpretation of the temporal development of RRT incidence in people with and without diabetes.

In another recent study, we analyzed the RRT incidence in people with and without diabetes in 2002–2016, using data from one regional German dialysis center (8). In this study, the IR did not change during the observation period either in the population with or in the population without diabetes. The incidence was ∼4.5 times higher among people with diabetes than among those without. However, the study population was too small to analyze age- and sex-specific time trends. Furthermore, the generalizability of those results to a nationwide population was limited. The aim of the current study, therefore, was *1*) to analyze the IR of RRT in Germany among people with and without diabetes as well as the corresponding RR and attributable risk to diabetes and *2*) to investigate time trends for the period 2010–2016 and analyze whether these patterns differ by age class and sex.

RESEARCH DESIGN AND METHODS

Study Design, Study Population, and Data Assessment

We pooled anonymized nationwide data of people who were insured at the two German branches of statutory health insurance companies—Allgemeine Ortskrankenkasse (AOK) (87% of the study population) and Betriebskrankenkasse (13%)—between 1 January 2009 and 31 December 2017. These data cover ∼25 million inhabitants (i.e., 30% of the German population) who were continuously insured in this period (i.e., ≤90-day gap) for at least 1 year, a prerequisite for defining the insured person's diabetes status. In Germany, health insurance is mandatory. Approximately 90% of the population in Germany are insured by statutory health insurance funds, while the remaining 10% are privately insured. Although there are several differences between the statutory and private system, both provide full-coverage health insurance, and German citizens have the same access to medical services, such as RRT.

Using an established algorithm (20), all people included in the study were classified as having diabetes if at least one of the following criteria was met: *1*) diagnosis of diabetes (ICD-10 codes E10–E14) in at least three of four consecutive quarters, *2*) at least two prescriptions of antihyperglycemic medications (Anatomical Therapeutic Chemical code A10) within 1 year, or *3*) at least one diagnosis of diabetes and prescription of an antihyperglycemic medication and one measurement of blood glucose or HbA_{1c} in the same quarter (to avoid false-positive cases as a result of data errors). We also included people with new-onset diabetes. These people were classified as having diabetes from the first quarter in which the diabetes criterion was fulfilled and retained their status throughout the study.

We identified all people with a first RRT between 1 January 2010 and 31 December 2016. Data from the years 2009 and 2017 were used only for the definition of RRT and diabetes (see below).

All cases of RRT among people with and without diabetes were recorded independently of the underlying reason for RRT. Chronic RRT was defined as chronic dialysis or preemptive kidney transplantation as indicators for treated ESRD. In line with a previous study (5), occurrence of dialysis was defined as at least one relevant physician service (i.e., hemodialysis, hemofiltration, peritoneal dialysis, hemodiafiltration) or related consultation fee arising from hospital or outpatient treatment. Dialysis was recorded as chronic dialysis if one of the following criteria was fulfilled: *1*) dialysis claims were documented at least once per week over a period of 12 consecutive weeks; *2*) dialysis $<$ 12 weeks was documented before a person died with an ESRD-relevant diagnosis in at least three subsequent quarters.

People with a "condition after transplantation" diagnosis were excluded if there had been no documented kidney transplantation during the observation period. Furthermore, we excluded people with RRT in 2009 or in the first year of their insurance period since only incident RRT in 2010–2016 was assessed.

Statistical Analysis

We conducted all analyses for the entire population as well as stratified by sex and age class using the age strata 0–39, 40–49, 50–59, 60–69, 70–79, and ≥80 years. IRs for chronic RRT were estimated by taking the number of first chronic RRT per person for each year of the observation period as the numerator and dividing by the cumulative PYs at risk from all insurance quarters of all insured people in the respective year minus those with a prevalent chronic RRT as the denominator. Stratum-specific and age- and sex-standardized IRs of chronic RRT were calculated with a 95% CI in the population with and without diabetes for each calendar year, using the German population of 2013 as a standard population with the aforementioned age strata. Furthermore, the

standardized IR of the population with and without diabetes was divided to calculate the IR ratios (IRRs) for each calendar year. We also calculated attributable risk among the population with diabetes and the population-attributable risk as a result of diabetes for each year to determine the percentage of people in whom RRT could theoretically be avoided if there were no exposure (i.e., diabetes).

To examine time trends, Poisson regression models were fitted with the IR of chronic RRT as the dependent variable for people with and without diabetes, both in the population as a whole and in the age and sex strata. Year of RRT (difference from 2010) was used as an independent variable to estimate the effect of calendar time. All models that were not stratified for age and/or sex were adjusted for these variables using the youngest age-group (<40 years) and female sex as a reference group. Furthermore, analogous Poisson models were fitted for the entire population, including a variable presence of diabetes (yes vs. no) and an interaction term "diabetes * year of RRT" to ascertain whether time trends differed significantly between the populations with and without diabetes.

To account for overdispersion of the outcome, we adjusted all models for descale on the basis of cumulated data on the covariate strata. We performed all analyses using SAS 9.4 TS1M1 for Windows (SAS Institute, Cary, NC).

Ethics

Neither individual written consent by patients nor ethical approval was required because the data were anonymous and no link to primary data was intended (21).

RESULTS

Study Population

The description of all insured people is presented in Table 1. Diabetes prevalence remained nearly constant (12.6% in 2010, 12.4% in 2016), with a somewhat higher proportion in women (13.2% vs. 12.5%).

We identified 73,638 people (44,196 men, 29,442 women) with a first chronic RRT in the period 2010–2016. About three-fifths of these people (men 59.3%, women 62.6%) had diabetes at the start of first chronic RRT, with proportions remaining stable throughout the study period.

The mean age at the start of chronic RRT was 71.3 years. People with diabetes were markedly older at the start of chronic RRT (73.0 years) than those without diabetes (68.6 years). The age at the start of chronic RRT increased slightly in people with diabetes from 72.6 to 73.5 years between 2010 and 2016 but decreased in people without diabetes from 69.2 to 67.6 years.

IR, RR, and Attributable Risk

Age- and sex-standardized IR, IRR, and attributable risks are shown for each calendar year in Table 2 and Fig. 1. The IR (per 100,000 PY) of chronic RRT in the population with diabetes was 135.0 (95% CI 124.7–145.3) in 2010, 110.2 (102.1–118.4) in 2013, and 106.7 (99.4–113.9) in 2016. We observed a substantially lower IR in the population without diabetes of 21.3 (20.7–21.9) in 2010, 18.4 (17.9–19.0) in 2013, and 19.7 (19.1–20.3) in 2016. The RR (IRR) comparing the RRT incidence between people with and without diabetes was 6.3 (95% CI 5.8–6.9) in 2010, 6.0 (5.5–6.5) in 2013, and 5.4 (5.0–5.8) in 2016. More than four-fifths of the incidence of chronic RRT in people with diabetes was attributable to diabetes. In the total population, almost one-half of chronic RRT incidence was attributable to diabetes. The IR was twice as high in men than in women, with greater differences in the subpopulation without diabetes than with diabetes. In contrast, the RR and attributable risk were higher in women. However, all observed trends were quite similar in both sexes.

Analysis of Time Trend in the Entire Population and Stratified by Age and Sex

The results of the incidence time trend from the fully adjusted Poisson models are shown in Table 3. The effect of calendar year in the population with and without diabetes is shown in models 1 and 2. We found a significant decrease in chronic RRT incidence in the population with diabetes during the observation period of 3% per year (RR per calendar year 0.972 [95% CI 0.965–0.979], $P < 0.0001$). We observed this trend in both sexes in almost all age classes (except men aged <40 years) (RR 0.998 [0.971–1.026], $P = 0.91$), although this decrease was not statistically significant in some age-groups.

No consistent temporal change was observed among the entire population without diabetes (RR 0.991 [95% CI 0.980–1.001], $P = 0.091$). The age- and sex-stratified analysis only revealed a significant decrease in incidence among women aged <40 years (0.977 [0.965–0.989], $P = 0.0003$) and in both sexes aged >80 years (0.982 [0.976–0.989], $P < 0.0001$).

Across the whole population (Supplementary Table 1, model 1), incidence of chronic RRT increased significantly with age, male sex, and diabetes (all $P < 0.0001$), the latter being true in all age and sex classes. No consistent changes were observed in the RRs between populations with and without diabetes as evidenced by the nonsignificant ($P = 0.29$) diabetes * calendar year interaction (Supplementary Table 1, model 2).

CONCLUSIONS

Main Findings

This study is one of only few large population-based studies to analyze the time trend of chronic RRT incidence in the population with and without diabetes, using the population with diabetes as a population at risk and recording all cases of chronic RRT irrespective of the underlying reason. IRs among people with diabetes were almost six times higher than in people without diabetes. A significant decrease in the incidence of chronic RRT was found during the observation period in people with diabetes independent of age and sex. However, no consistent time trend was observed in people without diabetes regarding age and sex.

Comparison With National Studies

In the current study, the IR in the populations with and without diabetes is in line with and somewhat higher, respectively, than the findings of another German study that analyzed claims data of one small insurance company in 2005/2006–2008 (5). Compared with our recent regional study analyzing data from

Table 1—Description of all people with first RRT and the background population, Germany, 2010–2016

						Men		Women	
Characteristic	Total	Men	Women	Diabetes	No diabetes	Diabetes	No diabetes	Diabetes	No diabetes
All years combined									
People with RRT	73,638	44,196	29,442	44,607 (60.6)	29,031 (39.4)	26,187 (59.3)	18,009 (40.7)	18,420 (62.6)	11,022 (37.4)
Age* (years)	71.3 (13.0)	70.1 (12.9)	73.0 (13.0)	73.0 (10.3)	68.6 (15.8)	71.7 (10.3)	67.8 (15.6)	74.9 (10.1)	69.8 (16.1)
<40	2,062	1,265	797	373 (18.1)	1,689 (81.9)	205 (16.2)	1,060 (83.8)	168 (21.1)	629 (78.9)
40–49	2,990	1,986	1,004	999 (33.4)	1,991 (66.6)	707 (35.6)	1,279 (64.4)	292 (29.1)	712 (70.9)
50–59	6,969	4,772	2,197	3,391 (48.7)	3,578 (51.3)	2,376 (49.8)	2,396 (50.2)	1,015 (46.2)	1,182 (53.8)
60–69	12,942	8,753	4,189	8,244 (63.7)	4,698 (36.3)	5,610 (64.1)	3,143 (35.9)	2,634 (62.9)	1,555 (37.1)
70–79	28,372	17,226	11,146	19,125 (67.4)	9,247 (32.6)	11,397 (66.2)	5,829 (33.8)	7,728 (69.3)	3,418 (30.7)
≥80	20,303	10,194	10,109	12,475 (61.4)	7,828 (38.6)	5,892 (57.8)	4,302 (42.2)	6,583 (65.1)	3,526 (34.9)
Year RRT started: 2010									
People with RRT	11,055	6,492	4,563	6,591 (59.6)	4,464 (40.4)	3,779 (58.2)	2,713 (41.8)	2,812 (61.6)	1,751 (38.4)
Age* (years)	71.2 (12.6)	69.8 (12.5)	73.2 (12.5)	72.6 (10.1)	69.2 (15.3)	71.0 (10.1)	68.2 (15.0)	74.7 (9.7)	70.7 (15.8)
Population at risk	23,662,600	11,218,907	12,443,693	2,985,436 (12.6)	20,677,165 (87.4)	1,372,354 (12.2)	9,846,553 (87.8)	1,613,082 (13.0)	10,830,611 (87.0)
Year RRT started: 2011									
People with RRT	10,854	6,474	4,380	6,619 (61.0)	4,235 (39.0)	3,864 (59.7)	2,610 (40.3)	2,755 (62.9)	1,625 (37.1)
Age* (years)	71.1 (12.9)	69.8 (12.9)	73.0 (12.7)	72.8 (10.2)	68.5 (15.9)	71.4 (10.2)	67.6 (15.8)	74.9 (9.9)	69.9 (15.9)
Population at risk	24,284,929	11,564,010	12,720,919	3,128,277 (12.9)	21,156,652 (87.1)	1,448,121 (12.5)	10,115,889 (87.5)	1,680,156 (13.2)	11,040,763 (86.8)
Year RRT started: 2012									
People with RRT	10,465	6,241	4,224	6,452 (61.7)	4,013 (38.3)	3,751 (60.1)	2,490 (39.9)	2,701 (63.9)	1,523 (36.1)
Age* (years)	71.6 (12.7)	70.5 (12.5)	73.2 (12.8)	73.1 (10.2)	69.2 (15.6)	71.8 (10.2)	68.6 (15.2)	74.9 (10.0)	70.2 (16.2)
Population at risk	24,606,706	11,765,762	12,840,944	3,220,715 (13.1)	21,385,991 (86.9)	1,498,549 (12.7)	10,267,214 (87.3)	1,722,167 (13.4)	11,118,777 (86.6)
Year RRT started: 2013									
People with RRT	10,075	6,032	4,043	6,213 (61.7)	3,862 (38.3)	3,656 (60.6)	2,376 (39.4)	2,557 (63.2)	1,486 (36.8)
Age* (years)	71.5 (12.9)	70.3 (12.7)	73.2 (13.1)	73.2 (10.4)	68.8 (15.9)	71.8 (10.3)	68.0 (15.5)	75.1 (10.2)	70.1 (16.4)
Population at risk	24,899,932	11,952,605	12,947,327	3,280,425 (13.2)	21,619,507 (86.8)	1,534,545 (12.8)	10,418,060 (87.2)	1,745,881 (13.5)	11,201,447 (86.5)
Year RRT started: 2014									
People with RRT	10,132	6,090	4,042	6,144 (60.6)	3,988 (39.4)	3,596 (59.0)	2,494 (41.0)	2,548 (63.0)	1,494 (37.0)
Age* (years)	71.3 (13.1)	70.3 (13.0)	72.8 (13.2)	73.1 (10.6)	68.7 (16.0)	71.9 (10.4)	68.1 (15.8)	74.7 (10.6)	69.6 (16.3)
Population at risk	25,475,526	12,257,432	13,218,094	3,335,648 (13.1)	22,139,878 (86.9)	1,566,635 (12.8)	10,690,797 (87.2)	1,769,013 (13.4)	11,449,081 (86.6)
Year RRT started: 2015									
People with RRT	10,495	6,398	4,097	6,278 (59.8)	4,217 (40.2)	3,793 (59.3)	2,605 (40.7)	2,485 (60.7)	1,612 (39.3)
Age* (years)	71.1 (13.2)	70.1 (13.1)	72.6 (13.1)	73.1 (10.4)	68.0 (16.0)	72.0 (10.4)	67.3 (15.9)	74.7 (10.2)	69.2 (16.0)
Population at risk	26,378,852	12,771,182	13,607,671	3,367,044 (12.8)	23,011,808 (87.2)	1,587,856 (12.4)	11,183,326 (87.6)	1,779,188 (13.1)	11,828,483 (86.9)
Year RRT started: 2016									
People with RRT	10,562	6,469	4,093	6,310 (59.7)	4,252 (40.3)	3,748 (57.9)	2,721 (42.1)	2,562 (62.6)	1,531 (37.4)
Age* (years)	71.1 (13.4)	70.0 (13.4)	72.9 (13.3)	73.5 (10.5)	67.6 (16.1)	72.2 (10.5)	66.8 (15.9)	75.3 (10.3)	68.9 (16.4)
Population at risk	27,476,848	13,384,263	14,092,585	3,394,440 (12.4)	24,082,409 (87.6)	1,606,163 (12.0)	11,778,100 (88.0)	1,788,276 (12.7)	12,304,309 (87.3)

Data are *n*, *n* (%), or, for age, mean (SD). *Measured at the start of RRT.

Table 2—RRT incidence Germany, 2010–2016

Variable	IR* (95% CI) per 100,000 PY					
	IRt	IRd	IRn	IRR	ARE	PAR
All years combined						
Total	35.5 (35.2–35.7)	114.1 (111.0–117.2)	19.6 (19.4–19.8)	5.8 (5.6–6.0)	0.83 (0.82–0.83)	0.45 (0.44–0.45)
Men	49.9 (49.4–50.4)	147.6 (142.5–152.7)	28.9 (28.5–29.3)	5.1 (4.9–5.3)	0.80 (0.80–0.81)	0.42 (0.41–0.43)
Women	24.2 (23.9–24.4)	84.7 (81.4–88.1)	12.6 (12.4–12.8)	6.7 (6.4–7.0)	0.85 (0.84–0.86)	0.48 (0.47–0.49)
Men and women stratified by year						
2010	38.3 (37.6–39.0)	135.0 (124.7–145.3)	21.3 (20.7–21.9)	6.3 (5.8–6.9)	0.84 (0.83–0.85)	0.44 (0.43–0.46)
2011	36.9 (36.2–37.6)	122.1 (113.2–130.9)	20.0 (19.4–20.6)	6.1 (5.6–6.6)	0.84 (0.82–0.85)	0.46 (0.45–0.46)
2012	35.2 (34.6–35.9)	114.9 (106.5–123.4)	19.0 (18.4–19.6)	6.0 (5.6–6.5)	0.83 (0.82–0.85)	0.46 (0.45–0.47)
2013	34.0 (33.3–34.6)	110.2 (102.1–118.4)	18.4 (17.9–19.0)	6.0 (5.5–6.5)	0.83 (0.82–0.85)	0.46 (0.45–0.47)
2014	34.0 (33.3–34.7)	109.1 (101.2–117.0)	19.0 (18.4–19.5)	5.8 (5.3–6.2)	0.83 (0.81–0.84)	0.44 (0.43–0.45)
2015	35.1 (34.4–35.8)	107.0 (99.7–114.2)	19.8 (19.2–20.5)	5.4 (5.0–5.8)	0.81 (0.80–0.83)	0.43 (0.43–0.44)
2016	34.9 (34.2–35.6)	106.7 (99.4–113.9)	19.7 (19.1–20.3)	5.4 (5.0–5.8)	0.82 (0.80–0.83)	0.43 (0.43–0.44)
Men						
2010	53.5 (52.1–54.8)	166.8 (151.6–182.0)	31.1 (29.9–32.2)	5.4 (4.9–5.9)	0.81 (0.79–0.83)	0.42 (0.40–0.43)
2011	52.1 (50.8–53.4)	156.3 (142.3–170.3)	29.5 (28.3–30.6)	5.3 (4.8–5.8)	0.81 (0.79–0.83)	0.43 (0.43–0.44)
2012	49.6 (48.4–50.9)	149.1 (135.2–163.1)	28.3 (27.2–29.5)	5.3 (4.8–5.8)	0.81 (0.79–0.83)	0.43 (0.42–0.44)
2013	47.9 (46.6–49.1)	142.2 (128.9–155.4)	27.1 (26.0–28.2)	5.3 (4.7–5.8)	0.81 (0.79–0.83)	0.43 (0.42–0.45)
2014	47.7 (46.5–48.9)	139.9 (126.6–153.2)	28.1 (27.0–29.2)	5.0 (4.5–5.5)	0.80 (0.78–0.82)	0.41 (0.40–0.42)
2015	49.5 (48.3–50.7)	139.7 (127.5–151.9)	28.8 (27.7–29.9)	4.9 (4.4–5.3)	0.79 (0.77–0.81)	0.42 (0.41–0.43)
2016	49.4 (48.2–50.6)	142.0 (129.2–154.7)	29.4 (28.3–30.5)	4.8 (4.4–5.3)	0.79 (0.77–0.81)	0.41 (0.39–0.42)
Women						
2010	26.3 (25.5–27.1)	107.8 (93.9–121.6)	13.8 (13.2–14.5)	7.8 (6.8–8.9)	0.87 (0.85–0.89)	0.47 (0.46–0.49)
2011	24.9 (24.2–25.7)	92.4 (81.8–103.0)	12.9 (12.2–13.5)	7.2 (6.3–8.1)	0.86 (0.84–0.88)	0.48 (0.47–0.49)
2012	24.1 (23.4–24.9)	85.1 (75.9–94.3)	12.1 (11.5–12.7)	7.0 (6.2–7.9)	0.86 (0.84–0.87)	0.50 (0.49–0.51)
2013	23.1 (22.4–23.9)	82.4 (73.2–91.6)	11.9 (11.3–12.5)	6.9 (6.1–7.8)	0.86 (0.84–0.87)	0.48 (0.47–0.50)
2014	23.3 (22.5–24.0)	81.8 (73.6–90.1)	12.1 (11.5–12.7)	6.8 (6.0–7.6)	0.85 (0.83–0.87)	0.48 (0.47–0.49)
2015	23.9 (23.1–24.6)	78.4 (70.7–86.2)	13.1 (12.4–13.7)	6.0 (5.4–6.7)	0.83 (0.81–0.85)	0.45 (0.44–0.46)
2016	23.5 (22.7–24.2)	75.1 (68.4–81.8)	12.3 (11.7–12.9)	6.1 (5.5–6.8)	0.84 (0.82–0.85)	0.48 (0.46–0.49)

IRR = IRd / IRn, where IRd is the cases of RRT in individuals with diabetes in the population with diabetes and IRn is the cases of RRT in individuals without diabetes in the population without diabetes. ARE, attributable risk of RRT because of diabetes among the population with diabetes ([IRd − IRn] / IRd); PAR, attributable risk of RRT because of diabetes in the total population ([IRt − IRn] / IRt), where IRt is all cases of RRT in the total population.*Standardized to the German population, 2013.

one regional German dialysis center (8) where no change of time trend was found, the IR of RRT in the current study is ∼1.3 times higher in both populations with and without diabetes, and thus, the RRs were very comparable. One possible explanation for the different findings between the two studies could be disparities between German health insurance funds and German regions with regard to insurant structures, health behaviors, and prevalence of diseases such as cardiovascular disease and diabetes (22–24). In particular, the increased RRT incidence in our study compared with the two previous German studies is due to the large proportion of study participants insured by the AOK. AOK is known to have a high proportion of insured persons with cardiovascular diseases and diabetes, a high number of people with migratory backgrounds, and a high number of people who smoke (24), all of which are known factors for the development of kidney disease and ESRD.

Comparison With International Studies

An international comparison with other studies is difficult since different methodological approaches were used among the studies. We found only a few epidemiological population-based studies with comparable study design regarding *1*) outcome (all cases of RRT and not only diabetic nephropathy as a primary reason for RRT) and *2*) denominator (population with diabetes as a population at risk [i.e., diabetes prevalence known or at least estimable]).

The age- and sex-standardized IR of chronic RRT in people with diabetes included in our study (114.1 per 100,000 PY) was fairly comparable with findings from Australia (93 per 100,000 PY) (18) and with results from Italy (17). Likewise, the age-adjusted RR comparing people with and without diabetes in our study was well in line with those observed in Italy (17).

The crude IR of chronic RRT among people with diabetes in our study was considerably lower (i.e., three to seven times) than those estimated in studies from Taiwan (11,25) and Hong Kong (16). However, comparability was limited by different definitions of outcomes and study populations. Interestingly, unlike our study, neither of the Asian studies identified a sex difference regarding incidence of chronic RRT (11,25).

Three studies reported time trend with contradictory results. The decrease in chronic RRT incidence in people with diabetes of 4% per year observed in the Hong Kong study between 2000 and 2012 was very comparable with our findings (16). In contrast, the 2004–2013 Italian study observed stable IRs in both populations with and without diabetes (17). Likewise, a study from Australia covering the years 2002–2013

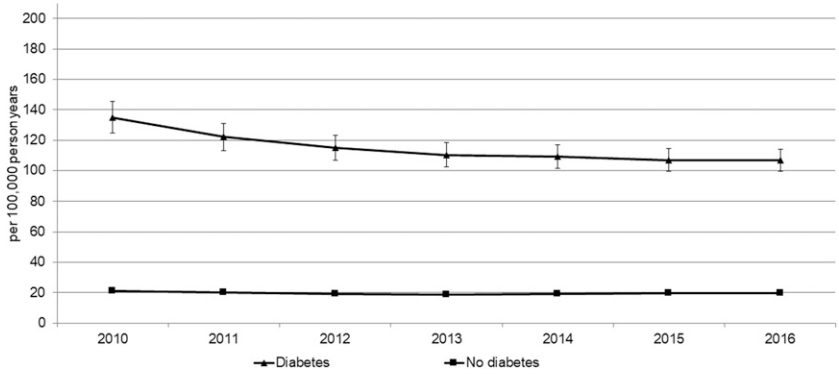

Figure 1—Time trend of age- and sex-standardized IRs of RRT, men and women.

reported a stable time trend in people with type 1 diabetes but a 4.5% increase per year in people with type 2 diabetes (18). This increase in people with type 2 diabetes may be explained by extended access to RRT or a greater willingness among elderly people with several comorbidities to start RRT.

Despite only having analyzed diabetic nephropathy as a reason for chronic RRT among people with diabetes, the findings of a large U.S. study are worthy of mention (7). Although diabetic nephropathy is the reason for chronic RRT in only 50% of people with type 2 diabetes, the age- and sex-adjusted IRs in the U.S. study were considerably higher than in the current study (260.2 per 100,000 PY in 2000, 173.9 per 100,000 PY in 2014). The reported decrease in IRs during the study period (2.8% reduction per year) was well in line with the declining incidence in the population with diabetes found in our study. It is remarkable that another U.S. study analyzing time trends of incidence of hospitalizations for ESRD found an increasing trend among young people with diabetes aged 18–45 years while the incidence has been plateauing in the age-groups >45 years since 2010 (19). An Australian study analyzing the age-specific time trend of chronic RRT incidence found a strong annual increase of 4.2% in the <50 and >80 age-groups among nonindigenous people, with no consistent time trend observed in the interim age-groups (18). In contrast, the decrease in incidence among people with diabetes identified in our study was more prominent in the younger age-groups, with the steepest decrease in women <40 years (12% reduction per year) and men aged 40–49 years (8% reduction per year). The observed decrease of chronic RRT incidence among people with diabetes in all age classes might partially be apportioned to improvements in diabetes care: better control of blood glucose, among others, therapy with sodium–glucose cotransporter 2 inhibitors, as well as early, adequate, and consistent therapy of hypertension with renin-angiotensin-aldosterone system blockers, and early diagnosis and treatment of kidney disease at an early stage in people with diabetes. This suggestion is confirmed by increasing age at the start of RRT during the study period (72.6 years in 2010, 73.5 years in 2016). Moreover, the increased number of people with diabetes participating in the disease management programs for type 1 and type 2 diabetes, which aim to prevent complications of diabetes, including ESRD, could also contribute to this favorable trend. A further explanation of this decline could be that more people with diabetes were detected at earlier stages of disease and, thus, had a lower risk of late complications of diabetes, including ESRD. In contrast, the time trend of incidence in the population without diabetes was age and sex dependent, with a significant decrease only in women aged <40 years and in men and women aged >80 years. The decrease observed among younger women could be a result of better compliance and regulation of blood pressure than in young men. The inconsistent time trend of RRT incidence in the middle-age-group might be explained by a late and insufficient treatment of hypertension, which leads to deterioration of renal function and, as a consequence, to vascular nephropathy. The declining rates among the elderly population could be explained by improvements in medical care for nephrological disorders. Another explanation could be that older patients with ESRD, who are often multimorbid, are treated without dialysis. Indirect support for the latter could be the decreasing age of patients without diabetes at the start of dialysis from 69.2 to 67.6 years during the study period.

Limitations and Strengths

Our study has some limitations. First, the claims data used potentially did not clearly distinguish between acute and chronic dialysis, particularly among people who died within 3 months of starting dialysis. To account for this, we developed an algorithm using a combination of physician services data for dialysis and clinical diagnosis relevant to chronic terminal renal disease. Second, we were unable to analyze important clinical variables, such as diabetes duration; clinical markers, such as glomerular filtration rate and blood pressure; and lifestyle factors, such as smoking. These variables are known prognostic factors for the development of ESRD among people with diabetes. Because of the highly sensitive nature of these personal data and current data protection legislation, physicians are not permitted to transfer such data to insurance companies. However, this data source does offer the advantage of providing a large number of cases, which allows for a population-based approach. Besides, the investigation of potentially explanatory factors was not the main objective of this study. Third, we were unable to distinguish between type 1 and type 2 diabetes with the current data set. However, since the majority of people with diabetes starting chronic RRT can be assumed to be people with type 2 diabetes, our findings are primarily true for a population with type 2 diabetes. Fourth, our study population is confined to two large statutory health insurance branches constituting ~30% of the German population. Because of sociodemographic and health-related differences between health insurance companies, the insured people included in the study may vary from those of other public and

Table 3—Results of Poisson models for people with and without diabetes: RRs for RRT, Germany, 2010–2016

	Both sexes		Men		Women	
	RR† (95% CI)	*P* value	RR† (95% CI)	*P* value	RR† (95% CI)	*P* value
Model 1 (population with diabetes)						
Year	0.972 (0.965–0.979)	<0.0001	0.973 (0.964–0.981)	<0.0001	0.971 (0.961–0.980)	<0.0001
Men vs. women	1.772 (1.720–1.825)	<0.0001	—	—	—	—
Age (years)*						
≥80	3.814 (3.252–4.472)	<0.0001	4.071 (3.355–4.939)	<0.0001	3.591 (2.926–4.407)	<0.0001
70–79	3.969 (3.387–4.650)	<0.0001	3.920 (3.235–4.749)	<0.0001	4.055 (3.305–4.974)	<0.0001
60–69	2.506 (2.135–2.942)	<0.0001	2.538 (2.091–3.080)	<0.0001	2.463 (2.000–3.034)	<0.0001
50–59	1.629 (1.381–1.922)	<0.0001	1.612 (1.322–1.965)	<0.0001	1.693 (1.361–2.105)	<0.0001
40–49	1.235 (1.028–1.485)	0.024	1.247 (1.004–1.547)	0.046	1.223 (0.949–1.577)	0.12
People aged <40 years only						
Year	0.945 (0.904–0.989)	0.016	0.998 (0.971–1.026)	0.91	0.884 (0.838–0.933)	<0.0001
Men vs. women	1.718 (1.432–2.061)	<0.0001	—	—	—	—
People aged 40–49 years only						
Year	0.933 (0.905–0.963)	<0.0001	0.917 (0.890–0.944)	<0.0001	0.975 (0.921–1.032)	0.38
Men vs. women	1.754 (1.530–2.012)	<0.0001	—	—	—	—
People aged 50–59 years only						
Year	0.970 (0.941–0.999)	0.046	0.973 (0.929–1.020)	0.26	0.962 (0.927–0.999)	0.042
Men vs. women	1.647 (1.446–1.875)	<0.0001	—	—	—	—
People aged 60–69 years only						
Year	0.972 (0.959–0.984)	<0.0001	0.966 (0.951–0.981)	<0.0001	0.983 (0.962–1.005)	0.13
Men vs women	1.782 (1.685–1.883)	<0.0001	—	—	—	—
People aged 70–79 years only						
Year	0.974 (0.962–0.986)	<0.0001	0.979 (0.966–0.992)	0.0018	0.967 (0.946–0.988)	0.0022
Men vs. women	1.671 (1.591–1.755)	<0.0001	—	—	—	—
People aged ≥80 years only						
Year	0.973 (0.962–0.985)	<0.0001	0.972 (0.958–0.986)	0.0001	0.974 (0.955–0.994)	0.012
Men vs. women	1.960 (1.868–2.056)	<0.0001	—	—	—	—
Model 2 (population without diabetes)						
Year	0.991 (0.980–1.001)	0.091	0.993 (0.983–1.002)	0.14	0.987 (0.977–0.997)	0.009
Men vs. women	2.313 (2.210–2.420)	<0.0001	—	—	—	—
Age (years)*						
≥80	39.492 (35.742–43.637)	<0.0001	48.587 (44.411–53.156)	<0.0001	28.279 (25.781–31.020)	<0.0001
70–79	27.160 (24.622–29.960)	<0.0001	30.524 (27.965–33.317)	<0.0001	21.499 (19.595–23.589)	<0.0001
60–69	12.505 (11.258–13.891)	<0.0001	13.954 (12.713–15.315)	<0.0001	10.045 (9.080–11.112)	<0.0001
50–59	6.355 (5.697–7.089)	<0.0001	6.845 (6.214–7.539)	<0.0001	5.516 (4.964–6.129)	<0.0001
40–49	3.485 (3.083–3.939)	<0.0001	3.578 (3.209–3.989)	<0.0001	3.325 (2.958–3.737)	<0.0001
People aged <40 years only						
Year	0.979 (0.960–0.998)	0.028	0.980 (0.946–1.014)	0.24	0.977 (0.965–0.989)	0.0003
Men vs. women	1.633 (1.508–1.768)	<0.0001	—	—	—	—
People aged 40–49 years only						
Year	1.011 (0.993–1.029)	0.22	1.016 (0.986–1.047)	0.29	1.002 (0.986–1.019)	0.78
Men vs. women	1.754 (1.629–1.890)	<0.0001	—	—	—	—
People aged 50–59 years only						
Year	1.005 (0.984–1.027)	0.64	1.006 (0.974–1.040)	0.70	1.003 (0.973–1.033)	0.86
Men vs. women	2.025 (1.848–2.220)	<0.0001	—	—	—	—
People aged 60–69 years only						
Year	0.995 (0.975–1.014)	0.58	0.996 (0.976–1.018)	0.73	0.991 (0.952–1.031)	0.65
Men vs. women	2.266 (2.085–2.464)	<0.0001	—	—	—	—
People aged 70–79 years only						
Year	0.987 (0.968–1.006)	0.17	0.987 (0.961–1.013)	0.31	0.987 (0.958–1.018)	0.42
Men vs. women	2.313 (2.142–2.498)	<0.0001	—	—	—	—
People aged ≥80 years only						
Year	0.982 (0.976–0.989)	<0.0001	0.987 (0.978–0.995)	0.0022	0.977 (0.968–0.986)	<0.0001
Men vs. women	2.805 (2.732–2.880)	<0.0001	—	—	—	—

*Baseline: <40 years.†RR per 1-year increment.

especially private health insurance companies (22–24). Therefore, the results can only be partially generalized to the entire German population. However, the estimated IRs in the populations both with and without diabetes and the corresponding RRs were comparable with those of both previous German studies (5,8). Finally, we analyzed the incidence of chronic RRT, which only counts cases of treated ESRD. It cannot be ruled out that some patients did not receive dialysis because of severe comorbidities, such as a threat of heart failure, or because of decisions against dialysis for religious or other personal reasons. However, all patients in Germany with an existing medical indication for dialysis have a statutory entitlement to dialysis.

A number of strengths should also be considered. First, our study is the first nationwide population-based study in Germany, covering almost one-third of the German population, to analyze the time trend of chronic RRT incidence among people with and without diabetes. Second, we were able to record all cases of chronic RRT in people with diabetes independently of their primary cause (i.e., not only diabetic nephropathy as a primary cause for chronic RRT). This is of note because especially in patients with type 2 diabetes, it is not always easy to distinguish between diabetic nephropathy as a main reason for ESRD and diabetes as a comorbidity when people with diabetes have coexisting diseases (e.g., hypertension or renal disease with nondiabetic pathogenesis) (26,27). Finally, we were able to estimate diabetes prevalence in the study population using an established algorithm. This methodological approach considers the increasing prevalence of diabetes in the population at risk (in contrast to IRs calculated in the general population) and, thus, allows a correct interpretation of results concerning the time trend.

In conclusion, the IR of RRT was six times higher in people with diabetes than in those without diabetes during the study period. The incidence of chronic RRT significantly decreased during the observation period in people with diabetes in all age and sex classes. In contrast, no consistent time trend was seen in people without diabetes with divergent age- and sex-specific results.

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ORIGINAL RESEARCH

Lower-extremity amputations in people with and without diabetes in Germany, 2008–2012 – an analysis of more than 30 million inhabitants

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Background and purpose: Lower-extremity amputations (LEAs) in people with diabetes are associated with reduced quality of life and increased health care costs. Detailed knowledge on amputation rates (ARs) is of utmost importance for future health care and economics strategies. We conducted the present cohort study in order to estimate the incidences of LEA as well as relative and attributable risk due to diabetes and to investigate time trends for the period 2008–2012.

Methods: On the basis of the administrative data from three large branches of German statutory health insurers, covering ~34 million insured people nationwide (about 40% of the German population), we estimated age-sex-standardized AR (first amputation per year) in the populations with and without diabetes for any, major, and minor LEAs. Time trends were analyzed using Poisson regression.

Results: A total of 108,208 individuals (diabetes: 67.3%; mean age 72.6 years) had at least one amputation. Among people with diabetes, we observed a significant reduction in major and minor ARs during 2008–2012 from 81.2 (95% CI 77.5–84.9) to 58.4 (55.0–61.7), and from 206.1 (197.3–214.8) to 177.0 (169.7–184.4) per 100,000 person-years, respectively. Among people without diabetes, the major AR decreased significantly from 14.3 (13.9–14.8) to 11.6 ([11.2–12.0], 12.0), whereas the minor AR increased from 15.8 (15.3–16.3) to 17.0 (16.5–17.5) per 100,000 person-years. The relative risk (RR) comparing the diabetic with the nondiabetic populations decreased significantly for both major and minor LEAs (4% and 5% annual reduction, respectively).

Conclusion: In this large nationwide population, we still found higher major and minor ARs among people with diabetes compared with those without diabetes. However, AR and RR of major and minor LEAs in the diabetic compared with the nondiabetic population decreased significantly during the study period, confirming a positive trend that has been observed in smaller and regional studies in recent years.

Keywords: diabetes, lower-extremity amputations, epidemiology, incidence, cohort study, relative risk, amputation rate, time trend

Introduction

The global prevalence of diabetes mellitus rose to 8.8% in 2015, which corresponds to 415 million people worldwide.[1] Consequently, the number of people with diabetic complications, including foot disease, has increased. Epidemiological studies have shown that up to 75% of lower-extremity amputations (LEAs) are performed in patients with diabetes.[2–4] Since LEA reduces quality of life[5] and increases medical costs,[6] various initiatives have been conceived to reduce the number of LEAs among

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people with diabetes.[7,8] In order to improve the quality of medical care among people with diabetes in Germany, disease management programs were introduced for type 2 diabetes in 2003 and for type 1 diabetes in 2005,[9] followed by a national guideline for the prevention and treatment of diabetic foot complications.[10]

Previous studies showed a large variation in incidence rates of LEA and relative risk (RR) among people with and without diabetes, as well as inconsistent results with respect to time trends.[2,4,11,12] The German Leverkusen Amputation Reduction Study (LARS)[2] began in the early 1990s and covered the population of the city of Leverkusen. It revealed a reduced incidence of LEA in the diabetic population between 1990 and 2005, but an unchanged incidence rate in the nondiabetic population. In the 1990s, the RR comparing people with and without diabetes in the LARS was 26 (95% CI 17–39).[13] A more recent study conducted in 2005–2007 using data from one statutory health insurance (SHI) found a considerably lower RR of 7.4 (95% CI 6.3–8.7).[3] However, nationwide data on incidence, RRs, and time trends of LEA in the diabetic and nondiabetic populations are lacking to date. Hence, the aim of this study was 1) to estimate the amputation rate (AR) of LEA stratified by amputation level in the population with and without diabetes as well as relative and attributable risk due to diabetes and 2) to investigate time trends for the period 2008–2012.

Methods

Study population and data assessment

We used anonymized nationwide pooled data from three German branches of SHI companies: Allgemeine Ortskrankenkasse (AOK) (68% of the study population), BARMER Ersatzkasse (25%), and Betriebskrankenkasse (7%), covering ~34 million inhabitants (ie, 42% of the German population). We included data from all individuals who were continuously insured (ie, ≤30 days gap in pairwise subsequent quarters by one of these SHI within the period January 1, 2007, to December 31, 2012) for at least 1 year, which was necessary to define the diabetes status of the insured individuals. Hence, individuals whose insurance period started later (eg, May 1, 2010) and fulfilled the above-mentioned inclusion criteria were also considered. Since diabetes mellitus not only is the leading cause of LEA due to diabetic neuropathy and arterial vascular disease but also contributes to the development of traumatic and cancer-related amputations.[14] We have taken into account all amputations between 2008 and 2012 irrespective of the potential causes of LEA, in line with Fosse et al.[14] In addition, insurance data from 2007 were used to ensure insurance periods of at least 1 year per person for insured individuals in 2008.

According to an established algorithm,[15] a "subject" was classified as having diabetes if at least one of the following criteria was met: 1) diagnosis of diabetes (ICD E10-E14) in at least three out of four consecutive quarters; 2) at least two prescriptions of antihyperglycemic medications (ATC code A10) within 1 year; or 3) at least one diagnosis of diabetes and prescription of an antidiabetic medication, one measurement of HbA_{1c}, or blood glucose in the same quarter (to avoid false-positive cases due to data errors). We also included patients with new-onset diabetes to meet the criteria during the entire observation period. A subject was classified as an "individual with diabetes" from the first quarter wherein the condition was fulfilled, and retained this status throughout the study.

Antihyperglycemic medication was assessed during the 6 months before a first amputation since 2008 (available only for patients with amputations).

We assessed LEA in 2008–2012 using the specific operation procedure codes (OPS) of the hospital discharge documentation.[3,16] We differentiated between major (OPS 5-864.x, 5-869.0: any LEA above the ankle joint) and minor amputation (OPS 5-865.x: through or distal to the ankle joint).[11,12,17]

Neither individual written consent by patients nor ethical approval was required as the data were anonymous and no link to primary data was intended.[18]

Statistical analysis

The main analyses were conducted for the entire population as well as sex-specifically for any LEAs as well as separately for major and minor amputations.

We estimated AR for each calendar year as follows: the number of any first LEA per individual occurring within this year – as numerator – was divided by the cumulative person-years (PY) at risk, from all insurance quarters of all insured individuals in the respective year – as denominator. Likewise, major and minor ARs were computed counting only first major and first minor amputations occurring within that year. The first major amputation occurring after a first minor amputation within each calendar year (which occurred frequently) was also counted for the analysis of major amputations.

We calculated direct age-sex-standardized AR for the entire population and age-standardized AR for sex-specific analysis using age strata 0–39, 40–49, 50–59, 60–69, 70–79, 80+ years, and the German population in 2010 as standard population. We estimated AR in the total population (ARt), among individuals with diabetes in the population with diabetes (ARd), and in subjects without diabetes in the population

without diabetes (ARn). We calculated amputation rate ratios (RR) by dividing the standardized AR of the populations with and without diabetes. Furthermore, we computed attributable risk among the population with diabetes (ARE) and population attributable risk due to diabetes (PAR) along with 95% CI in order to describe what proportion of amputations could theoretically be avoided if the exposure (ie, diabetes) was omitted.[19]

To test for time trend, we fitted Poisson regression models, since our outcome variable AR is a counting variable per PY, using year of amputation (difference from 2008) to estimate the effect of calendar time. All models were adjusted for overdispersion, with Pearson scale as correction factor for the total population. The choice of this regression model was justified by the application of goodness-of-fit tests, which showed the best fit for this approach.[20] We further adjusted all models for age, sex, and diabetes status as independent variables. Besides this, we stratified all models by diabetes status and sex. In addition, we performed models including interaction between diabetes and year of amputation, age, and sex.

Data were evaluated using the Statistical Analysis System SAS (SAS for Windows 7, Release 9.4 TS1M1; SAS Institute Inc., Cary, NC, USA).

Results

Study population

The description of all insured individuals is shown in Table 1. In the period 2008–2012, ~34 million people received SHI continuously from three insurers (2008: 32,916,390 PY, 2012: 34,136,653 PY). Approximately 11% (2008: 10.6%, 2012: 11.9%) of all insured individuals were classified as patients with diabetes with similar numbers among both sexes, with a proportion of insured men of about 46% (2008: 45.4%, 2012: 46.1%).

In total, 108,208 individuals (66,721 men, 41,487 women) underwent at least one amputation between 2008 and 2012, of whom 77,929 (50,298 men, 27,631 women) underwent at least one minor amputation and 45,414 (26,583 men, 18,831 women) at least one major amputation. The minor-to-major ratio increased from 1.64 in 2008 to 2.13 in 2012 with considerably higher ratios among the men.

Mean age at the time of first any amputation (N=108,208) between 2008 and 2012 was 72.6 years (SD 12.8), with women being considerably older (77.2 years, SD 12.6) than men (69.7 years, SD 12.1). The age at amputation remained nearly stable among both sexes. About two thirds (N=72,782) of all persons with amputation had diabetes (men: 68.9%, women: 64.6%). This proportion remained nearly stable between 2008 and 2012. Among people with diabetes and amputation, insulin therapy was recorded by 40%, oral therapy by 23.0%, and a combination of insulin and oral treatment therapy by 15.9%. Accordingly, 21.5% of these patients had no prescription of any antihyperglycemic medication. This distribution was similar in men and women.

AR, relative and attributable risk

Age- and age-sex-standardized AR as well as RR, ARE, and PAR for each calendar year are shown in Table 2 and Figure 1. We observed a consistent reduction in the AR among the population with diabetes over time: 258.6 (95% CI 249.4–267.7) per 100,000 PY in 2008, and 216.2 (208.4–224.1) in 2012. In contrast, the AR in the population without diabetes slightly decreased: 27.9 (27.3–28.5) per 100,000 PY to 26.6 (26.0–27.2). Thus, the RR decreased considerably from 9.3 (8.9–9.7) in 2008 to 8.1 (7.8–8.5) in 2012. Likewise, the ARE decreased from 89.2% (88.8%–89.7%) to 87.7% (87.2%–88.2%), whereas the PAR remained nearly stable at 58%.

The age-standardized AR was two- to threefold higher among men compared with women, which was true for individuals with and without diabetes. With regard to time trend, RR, ARE, and PAR, we observed similar results in both sexes.

The age-sex-standardized major AR decreased strongly in the diabetic population, with a major AR of 81.2 (77.5–84.9) per 100,000 PY in 2008 and 58.4 (55.0–61.7) in 2012. This was also evident in the nondiabetic population, decreasing from 14.3 (13.9–14.8) in 2008 to 11.6 (11.2–12.0) per 100,000 PY in 2012. The RR decreased from 5.7 (5.4–6.0) in 2008 to 5.1 (4.7–5.4) in 2012. A similar pattern was observed for both attributable risks, decreasing from 82% to 80% among the population with diabetes and 48% to 46% among the total population.

We observed more than double the age-standardized major AR in men compared with women in both diabetic and nondiabetic populations, with similar results regarding time trends. The decrease in RR, ARE, and PAR was only prominent among women.

The age-sex-standardized minor AR between 2008 and 2012 in the population with diabetes decreased considerably from 206.1 (197.3–214.8) per 100,000 PY to 177.0 (169.7–184.4), while among the population without diabetes the minor AR increased from 15.8 (15.3–16.3) to 17.0 (16.5–17.5) per 100,000 PY. Hence, we observed a strong reduction in the RR from 13.1 (12.4–13.8) in 2008 to 10.4 (9.9–11.0) in 2012. Likewise, we detected a moderate reduction in ARE (92% to 90%) and PAR (66% to 64%) for the period between 2008 and 2012.

Table 1 Description of all statutory health insurants with amputation[a] and the background population in Germany, 2008–2012

Characteristics	Total	Men	Women	Diabetes
Year of amputation: 2008				
Number of amputations (%)	25,183 (100.0)	15,522 (61.6)	9,661 (38.4)	17,284 (68.6)
Person years (%)	32,916,390 (100.0)	14,938,723 (45.4)	17,977,667 (54.6)	3,489,865 (10.6)
Mean age[b] (years, SD)	72.2 (12.7)	69.2 (11.8)	77.1 (12.4)	72.4 (10.9)
Number of amputations by type				
Major amputation (%)	10,599 (100.0)	6,080 (57.4)	4,519 (42.6)	6,511 (61.4)
Minor amputation (%)	17,412 (100.0)	11,336 (65.1)	6,076 (34.9)	12,982 (74.6)
Minor to major ratio	1.64	1.86	1.34	1.99
Year of amputation: 2009				
Number of amputations (%)	25,579 (100.0)	15,979 (62.5)	9,600 (37.5)	17,830 (69.7)
Person years	33,337,798 (100.0)	15,215,121 (45.6)	18,122,677 (54.4)	3,645,728 (10.9)
Mean age[b] (years, SD)	72.3 (12.6)	69.5 (11.9)	77 (12.3)	72.6 (10.8)
Number of amputations by type				
Major amputation (%)	10,383 (100.0)	6,100 (58.7)	4,283 (41.3)	6,497 (62.6)
Minor amputation (%)	17,909 (100.0)	11,691 (65.3)	6,218 (34.7)	13,476 (75.2)
Minor to major ratio	1.72	1.92	1.45	2.07
Year of amputation: 2010				
Number of amputations (%)	25,402 (100.0)	16,070 (63.3)	9,332 (36.7)	17,677 (69.6)
Person years	34,129,450 (100.0)	15,674,261 (45.9)	18,455,190 (54.1)	3,802,807 (11.1)
Mean age[b] (years, SD)	72.3 (12.6)	69.6 (11.7)	77 (12.6)	72.7 (11.0)
Number of amputations by type				
Major amputation (%)	9,533 (100.0)	5,612 (58.9)	3,921 (41.1)	5,924 (62.1)
Minor amputation (%)	18,293 (100.0)	12,100 (66.1)	6,193 (33.9)	13,659 (74.7)
Minor to major ratio	1.92	2.16	1.58	2.31
Year of amputation: 2011				
Number of amputations (%)	25,383 (100.0)	16,238 (64.0)	9,145 (36.0)	17,695 (69.7)
Person years	34,893,178 (100.0)	16,104,953 (46.2)	18,788,226 (53.8)	3,959,719 (11.3)
Mean age[b] (years, SD)	72.4 (12.6)	69.9 (11.8)	76.8 (12.7)	72.8 (10.9)
Number of amputations by type				
Major amputation (%)	9,089 (100.0)	5,438 (59.8)	3,651 (40.2)	5,617 (61.8)
Minor amputation (%)	18,663 (100.0)	12,436 (66.6)	6,227 (33.4)	13,907 (74.5)
Minor to major ratio	2.05	2.29	1.71	2.48
Year of amputation: 2012				
Number of amputations (%)	24,897 (100.0)	15,949 (64.1)	8,948 (35.9)	17,272 (69.4)
Person years	34,136,653 (100.0)	15,745,326 (46.1)	18,391,328 (53.9)	4,047,497 (11.9)
Mean age[b] (years, SD)	72.7 (12.6)	70.3 (11.9)	77 (12.7)	73.1 (11.0)
Number of amputations by type				
Major amputation (%)	8,699 (100.0)	5,243 (60.3)	3,456 (39.7)	5,368 (61.7)
Minor amputation (%)	18,512 (100.0)	12,267 (66.3)	6,245 (33.7)	13,665 (73.8)
Minor to major ratio	2.13	2.34	1.81	2.55

Notes: [a]Only first amputation per year counted. [b]Age at time of first amputation.

The age-standardized minor AR was about threefold higher in men compared with women, with nearly identical results regarding time trends, RR and ARE. Only PAR was significantly higher among men compared with women (Table 2).

Analysis of time trend and other covariates

The results of the fully adjusted Poisson models for the investigation of time trends are presented in Table 3. We observed a significant reduction in any AR of 4% per year in the population with diabetes, which was stronger among women compared with men: RR per calendar year was 6% and 3%, respectively. In contrast, among the population without diabetes, this rate remained nearly constant without gender differences (Figure 1A). In the Poisson model, which additionally included interaction terms with diabetes, we observed a significant reduction of 3% per year in RR between the populations with and without diabetes (RR per calendar year 0.97; 95% CI 0.95–0.99) without gender differences. With regard to the whole study period, the RR between the populations with and without diabetes strongly

No diabetes	Men		Women	
	Diabetes	No diabetes	Diabetes	No diabetes
7,899 (31.4)	10,890 (70.2)	4,632 (29.8)	6,394 (66.2)	3,267 (33.8)
29,426,525 (89.4)	1,570,129 (10.5)	13,368,594 (89.5)	1,919,736 (10.7)	16,057,931 (89.3)
71.8 (15.7)	69.7 (10.2)	67.9 (14.9)	76.9 (10.7)	77.4 (15.2)
4,088 (38.6)	3,787 (62.3)	2,293 (37.7)	2,724 (60.3)	1,795 (39.7)
4,430 (25.4)	8,573 (75.6)	2,763 (24.4)	4,409 (72.6)	1,667 (27.4)
1.08	2.26	1.20	1.62	0.93
7,749 (30.3)	11,420 (71.5)	4,559 (28.5)	6,410 (66.8)	3,190 (33.2)
29,692,070 (89.1)	1,650,261 (10.8)	13,564,859 (89.2)	1,995,467 (11.0)	16,127,210 (89.0)
71.8 (15.8)	70.2 (10.2)	67.9,(15.2)	76.8 (10.7)	77.3 (15.1)
3,886 (37.4)	3,880 (63.6)	2,220 (36.4)	2,617 (61.1)	1,666 (38.9)
4,433 (24.8)	8,983 (76.8)	2,708 (23.2)	4,493 (72.3)	1,725 (27.7)
1.14	2.32	1.22	1.72	1.04
7,725 (30.4)	11,411 (71.0)	4,659 (29.0)	6,266 (67.1)	3,066 (32.9)
30,326,644 (88.9)	1,732,025 (11.1)	13,942,236 (88.9)	2,070,781 (11.2)	16,384,408 (88.8)
71.4 (15.5)	70.3 (10.3)	68.0 (14.4)	77.1 (10.8)	76.6 (15.6)
3,609 (37.9)	3,512 (62.6)	2,100 (37.4)	2,412 (61.5)	1,509 (38.5)
4,634 (25.3)	9,196 (76.0)	2,904 (24.0)	4,463 (72.1)	1,730 (27.9)
1.28	2.62	1.38	1.85	1.15
7,688 (30.3)	11,653 (71.8)	4,585 (28.2)	6,042 (66.1)	3,103 (33.9)
30,933,459 (88.7)	1,809,848 (11.2)	14,295,105 (88.8)	2,149,871 (11.4)	16,638,355 (88.6)
71.4 (15.8)	70.6 (10.3)	68 (14.9)	77.1 (10.8)	76.4 (15.8)
3,472 (38.2)	3,436 (63.2)	2,002 (36.8)	2,181 (59.7)	1,470 (40.3)
4,756 (25.5)	9,484 (76.3)	2,952 (23.7)	4,423 (71.0)	1,804 (29.0)
1.37	2.76	1.47	2.03	1.23
7,625 (30.6)	11,396 (71.5)	4,553 (28.5)	5,876 (65.7)	3,072 (34.3)
30,089,156 (88.1)	1,854,163 (11.8)	13,891,162 (88.2)	2,193,334 (11.9)	16,197,994 (88.1)
71.7 (15.6)	71.1 (10.4)	68.2 (14.9)	77.1 (11.1)	76.8 (15.3)
3,331 (38.3)	3,343 (63.8)	1,900 (36.2)	2,025 (58.6)	1,431 (41.4)
4,847 (26.2)	9,258 (75.5)	3,009 (24.5)	4,407 (70.6)	1,838 (29.4)
1.46	2.77	1.58	2.18	1.28

decreased with increasing age (RR 80+ years vs 0–39 years: 0.11; 95% CI 0.08–0.13), with comparable results in both sexes (data not shown).

When repeating this analysis for major amputation, we observed a substantially stronger significant reduction in the major AR of 9% per year in the population with diabetes with a somewhat stronger decline among women compared with men (11% and 8%, respectively). Likewise, we observed a significant, albeit weaker, reduction in this rate of 6% per year among the population without diabetes, with comparable results in both sexes (Figure 1B). In the model including interaction terms, we observed a significant reduction of 4% per year in RR comparing the populations with and without diabetes (RR per calendar year 0.96; 95% CI 0.94–0.98), which was comparable in both sexes (data not shown).

Regarding the minor AR among people with diabetes, we observed a significantly reduced time trend – by 3% per year with quite similar results in both sexes. In contrast, there was a moderate but significant increase in this rate (2% per year) in the population without diabetes, with similar results across sexes (Figure 1C). Again, we observed a significant reduction of 5% per year in the RR between the populations

Table 2 Amputation rate among people with and without diabetes in Germany, 2008–2012

Calendar year	Amputation rate[a] (95% CI) per 100,000 person years			Relative and attributable risk (95% CI)		
	ARt	ARd	ARn	RR	ARE	PAR
Any amputation						
Total population						
Calendar year						
2008	66.9 (66.0–67.7)	258.6 (249.4–267.7)	27.9 (27.3–28.5)	9.3 (8.9–9.7)	0.89 (0.89–0.90)	0.58 (0.58–0.59)
2009	67.0 (66.2–67.8)	252.6 (243.6–261.5)	27.3 (26.7–27.9)	9.2 (8.9–9.6)	0.89 (0.89–0.90)	0.59 (0.58–0.6)
2010	65.2 (64.4–66)	235.7 (227.9–243.6)	27.0 (26.4–27.6)	8.7 (8.4–9.1)	0.89 (0.88–0.89)	0.59 (0.58–0.59)
2011	63.9 (63.1–64.7)	224.3 (216.7–231.9)	26.6 (26–27.2)	8.5 (8.1–8.8)	0.88 (0.88–0.89)	0.58 (0.58–0.59)
2012	62.5 (61.7–63.3)	216.2 (208.4–224.1)	26.6 (26–27.2)	8.1 (7.8–8.5)	0.88 (0.87–0.88)	0.57 (0.57–0.58)
Men						
Calendar year						
2008	101.7 (100.0–103.3)	379.4 (363.6–395.2)	41.2 (40.0–42.5)	9.2 (8.7–9.7)	0.89 (0.89–0.90)	0.59 (0.58–0.6)
2009	102.9 (101.3–104.5)	371.9 (356.8–387.1)	40.4 (39.2–41.6)	9.2 (8.8–9.7)	0.89 (0.89–0.90)	0.61 (0.60–0.62)
2010	100.8 (99.2–102.3)	348.0 (334.8–361.2)	40.5 (39.3–41.6)	8.6 (8.2–9.0)	0.88 (0.88–0.89)	0.60 (0.59–0.61)
2011	99.5 (97.9–101.0)	337.8 (324.6–351.0)	39.4 (38.2–40.6)	8.6 (8.2–9.0)	0.88 (0.88–0.89)	0.60 (0.59–0.61)
2012	97.4 (95.9–98.9)	323.2 (309.5–337.0)	39.4 (38.2–40.6)	8.2 (7.8–8.6)	0.88 (0.87–0.88)	0.60 (0.59–0.61)
Women						
Calendar year						
2008	37.5 (36.8–38.3)	149.3 (140.3–158.3)	16.7 (16.2–17.3)	8.9 (8.3–9.6)	0.89 (0.88–0.90)	0.55 (0.54–0.57)
2009	37.1 (36.3–37.8)	146.1 (136.7–155.4)	16.4 (15.9–17.0)	8.9 (8.3–9.6)	0.89 (0.88–0.90)	0.56 (0.54–0.57)
2010	35.6 (34.8–36.3)	135.3 (126.7–143.8)	15.8 (15.2–16.4)	8.6 (8.0–9.2)	0.88 (0.87–0.89)	0.56 (0.54–0.57)
2011	34.5 (33.8–35.2)	123.1 (115.6–130.6)	16.0 (15.4–16.6)	7.7 (7.2–8.3)	0.87 (0.86–0.88)	0.54 (0.52–0.55)
2012	33.9 (33.2–34.6)	121.6 (114.2–129.0)	16.0 (15.4–16.6)	7.6 (7.1–8.2)	0.87 (0.86–0.88)	0.53 (0.51–0.54)
Major amputation						
Total population						
Calendar year						
2008	27.6 (27.1–28.1)	81.2 (77.5–84.9)	14.3 (13.9–14.8)	5.7 (5.4–6.0)	0.82 (0.81–0.83)	0.48 (0.47–0.49)
2009	26.7 (26.2–27.2)	82.1 (77.5–86.6)	13.7 (13.2–14.1)	6.0 (5.6–6.4)	0.83 (0.82–0.84)	0.49 (0.48–0.50)
2010	24.0 (23.6–24.5)	68.6 (65.2–72.0)	12.6 (12.2–13.0)	5.5 (5.1–5.8)	0.82 (0.81–0.83)	0.48 (0.46–0.49)
2011	22.5 (22.0–23.0)	62.0 (59.0–65.1)	12.0 (11.6–12.4)	5.2 (4.9–5.5)	0.81 (0.80–0.82)	0.47 (0.45–0.48)
2012	21.5 (21.1–22.0)	58.4 (55.0–61.7)	11.6 (11.2–12)	5.1 (4.7–5.4)	0.80 (0.79–0.82)	0.46 (0.45–0.48)
Men						
Calendar year						
2008	39.9 (38.9–41.0)	111.8 (105.7–117.8)	20.4 (19.6–21.3)	5.5 (5.1–5.9)	0.82 (0.81–0.83)	0.49 (0.47–0.51)

(*Continued*)

Table 2 (*Continued*)

Calendar year	Amputation rate[a] (95% CI) per 100,000 person years			Relative and attributable risk (95% CI)		
	ARt	ARd	ARn	RR	ARE	PAR
2009	39.5 (38.5–40.5)	114.7 (107.3–122.1)	19.7 (18.9–20.5)	5.8 (5.4–6.3)	0.83 (0.82–0.84)	0.50 (0.48–0.52)
2010	35.3 (34.3–36.2)	96.8 (91.3–102.3)	18.3 (17.5–19.0)	5.3 (4.9–5.7)	0.81 (0.8–0.82)	0.48 (0.47–0.50)
2011	33.4 (32.5–34.3)	88.2 (83.6–92.7)	17.3 (16.5–18.0)	5.1 (4.8–5.5)	0.80 (0.79–0.82)	0.48 (0.46–0.50)
2012	32.0 (31.1–32.9)	84.6 (79.0–90.2)	16.4 (15.6–17.1)	5.2 (4.8–5.6)	0.81 (0.79–0.82)	0.49 (0.47–0.51)
Women						
Calendar year						
2008	17.0 (16.5–17.6)	54.4 (50.1–58.7)	9.1 (8.7–9.5)	6.0 (5.5–6.6)	0.83 (0.82–0.85)	0.47 (0.45–0.49)
2009	16.1 (15.6–16.6)	53.9 (48.4–59.3)	8.5 (8.1–8.9)	6.3 (5.7–7.1)	0.84 (0.82–0.86)	0.47 (0.45–0.49)
2010	14.5 (14.0–15.0)	43.7 (39.6–47.8)	7.7 (7.3–8.1)	5.7 (5.1–6.3)	0.83 (0.81–0.84)	0.47 (0.45–0.49)
2011	13.4 (13.0–13.9)	39.2 (35.0–43.3)	7.5 (7.2–7.9)	5.2 (4.6–5.8)	0.81 (0.78–0.83)	0.44 (0.42–0.46)
2012	12.8 (12.4–13.2)	35.5 (31.8–39.1)	7.4 (7.0–7.8)	4.8 (4.3–5.4)	0.79 (0.77–0.81)	0.42 (0.40–0.44)
Minor amputation						
Total population						
Calendar year						
2008	46.8 (46.1–47.5)	206.1 (197.3–214.8)	15.8 (15.3–16.3)	13.1 (12.4–13.8)	0.92 (0.92–0.93)	0.66 (0.65–0.67)
2009	47.3 (46.6–48.0)	198.9 (190.7–207.2)	15.7 (15.2–16.2)	12.7 (12.0–13.3)	0.92 (0.92–0.93)	0.67 (0.66–0.68)
2010	47.4 (46.7–48.1)	189.5 (182.1–196.9)	16.3 (15.8–16.7)	11.7 (11.1–12.2)	0.91 (0.91–0.92)	0.66 (0.65–0.67)
2011	47.3 (46.6–48.0)	181.7 (174.6–188.9)	16.5 (16.0–17.0)	11.0 (10.5–11.6)	0.91 (0.91–0.91)	0.65 (0.64–0.66)
2012	46.7 (46.0–47.4)	177.0 (169.7–184.4)	17.0 (16.5–17.5)	10.4 (9.9–11.0)	0.90 (0.90–0.91)	0.64 (0.63–0.65)
Men						
Calendar year						
2008	74.0 (72.7–75.4)	312.0 (296.7–327.3)	24.6 (23.7–25.6)	12.7 (11.9–13.5)	0.92 (0.92–0.93)	0.67 (0.66–0.68)
2009	75.0 (73.7–76.4)	300.0 (285.8–314.2)	24.0 (23.1–24.9)	12.5 (11.8–13.3)	0.92 (0.92–0.93)	0.68 (0.67–0.69)
2010	75.7 (74.4–77.1)	287.1 (274.5–299.8)	25.3 (24.3–26.2)	11.4 (10.7–12.0)	0.91 (0.91–0.92)	0.67 (0.66–0.68)
2011	76.0 (74.7–77.4)	279.5 (267.0–292.1)	25.4 (24.4–26.3)	11.0 (10.4–11.7)	0.91 (0.90–0.91)	0.67 (0.66–0.68)
2012	74.9 (73.5–76.2)	267.9 (254.9–280.8)	26.1 (25.2–27.0)	10.3 (9.7–10.9)	0.90 (0.90–0.91)	0.65 (0.64–0.66)
Women						
Calendar year						
2008	24.1 (23.5–24.7)	110.0 (101.8–118.3)	8.7 (8.2–9.1)	12.7 (11.6–13.9)	0.92 (0.91–0.93)	0.64 (0.63–0.66)
2009	24.5 (23.8–25.1)	108.4 (100.2–116.6)	9.0 (8.6–9.4)	12.1 (11.0–13.2)	0.92 (0.91–0.92)	0.63 (0.62–0.65)
2010	24.0 (23.4–24.6)	102.2 (94.4–109.9)	9.0 (8.6–9.4)	11.3 (10.4–12.4)	0.91 (0.90–0.92)	0.62 (0.61–0.64)

(*Continued*)

Table 2 (*Continued*)

Calendar year	Amputation rate[a] (95% CI) per 100,000 person years			Relative and attributable risk (95% CI)		
	ARt	ARd	ARn	RR	ARE	PAR
2011	23.8 (23.2–24.4)	94.7 (88.1–101.3)	9.3 (8.9–9.8)	10.2 (9.3–11.0)	0.90 (0.89–0.91)	0.61 (0.59–0.62)
2012	23.9 (23.3–24.5)	96.8 (90.0–103.6)	9.6 (9.2–10.1)	10.1 (9.3–11.0)	0.90 (0.89–0.91)	0.60 (0.58–0.61)

Note: [a]Age–sex (both sexes together) and age (men and women separate) standardized to the German population 2010.
Abbreviations: ARt, amputation rate in total population; ARd, amputation rate in individuals with diabetes in population with diabetes; ARn, amputation rate in individuals without diabetes in population without diabetes; RR, relative risk (ARd/ARn); ARE, attributable risk of diabetes among the population with diabetes; PAR, population attributable risk due to diabetes.

with and without diabetes (RR per calendar year 0.95; 95% CI 0.94–0.97) when estimated using interaction terms with similar results across sexes.

Discussion

This nationwide study covering >40% of the German population presents the ARs and RRs of LEA in the populations with and without diabetes between 2008 and 2012. The ARs were considerably higher among the population with diabetes compared with the population without diabetes, with particularly high RRs for minor amputation. The major ARs markedly decreased in both populations. In contrast, minor ARs decreased only in the population with diabetes, and even slightly increased in the population without diabetes. RRs between the populations with and without diabetes decreased significantly during the study period for both major and minor LEA. ARs increased strongly with age and were two- to threefold higher in men than in women.

Methodological discrepancies in the study design make any comparison between studies extremely difficult.[21] Some studies analyzed any LEA,[14,22,23] while another reported the incidence of LEA stratified by anatomical level.[4,11,13] Moreover, studies that counted only one LEA per person[3,4,14,17] cannot be compared with studies that counted several LEAs per person.[11,12] Therefore, some important criteria regarding the interpretation of the study results should be taken into account: anatomic definition of LEA (major/minor LEA); cause of LEA (if traumatic and/or cancer-related, LEA were included or excluded); recording of LEA (one or more LEAs per person were analyzed); and characteristics of the study population and population at risk. In epidemiological studies, often the incidence rate of the first amputation is counted (first lifetime amputation or first amputation during the study period or at least the first amputation of the year) to avoid bias when predictors or time trends are analyzed. Amputations in a person are not independent events; it is well known that the first amputation is a significant predictor of subsequent amputations.[24] In this study, we counted the first amputation per person per calendar year, which means that a re-amputation occurring in a subsequent year would also be counted. For this reason, the AR is higher compared with studies that counted only first lifetime LEAs or first LEAs during the study period. Furthermore, we recorded all LEAs regardless of their cause. We were able to define the at-risk diabetic population completely, including people without anti-hyperglycemic medication, and took into account those with new-onset diabetes during the study period.

We found a reduction of 4% per year in the AR in the population with diabetes, with a stronger decline among women. In the nondiabetic population, AR remained almost constant, without significant gender differences. The RR of any LEA between the populations with and without diabetes during the study period decreased substantially, reaching 8.1 in 2012. The observed effect could be explained principally by the reduction in the absolute number of amputations and major AR among people with diabetes (see below).

Our results indicate a further reduction in the incidence of LEA among people with diabetes and in the relative LEA risk that were described previously in the LARS.[2] However, our findings regarding AR are somewhat higher compared with the 2005–2007 German study based on SHI data (Gmünder Ersatzkasse [GEK]).[3] The main reason for this is that while we counted one LEA per calendar year, the earlier studies counted only one per person, which means that the figures are not comparable. Furthermore, GEK-insured individuals had lower prevalence of diabetes than those from AOK,[25] which was the source of some two thirds of the study population. Moreover, the relatively lower number of insured individuals (1.6 million members) and corresponding lower absolute number of LEAs in the previous studies should be taken into account by the comparison. Our results with respect to AR in the diabetic as well as the nondiabetic populations are higher compared with other European countries,[4,14] possibly due to a differ-

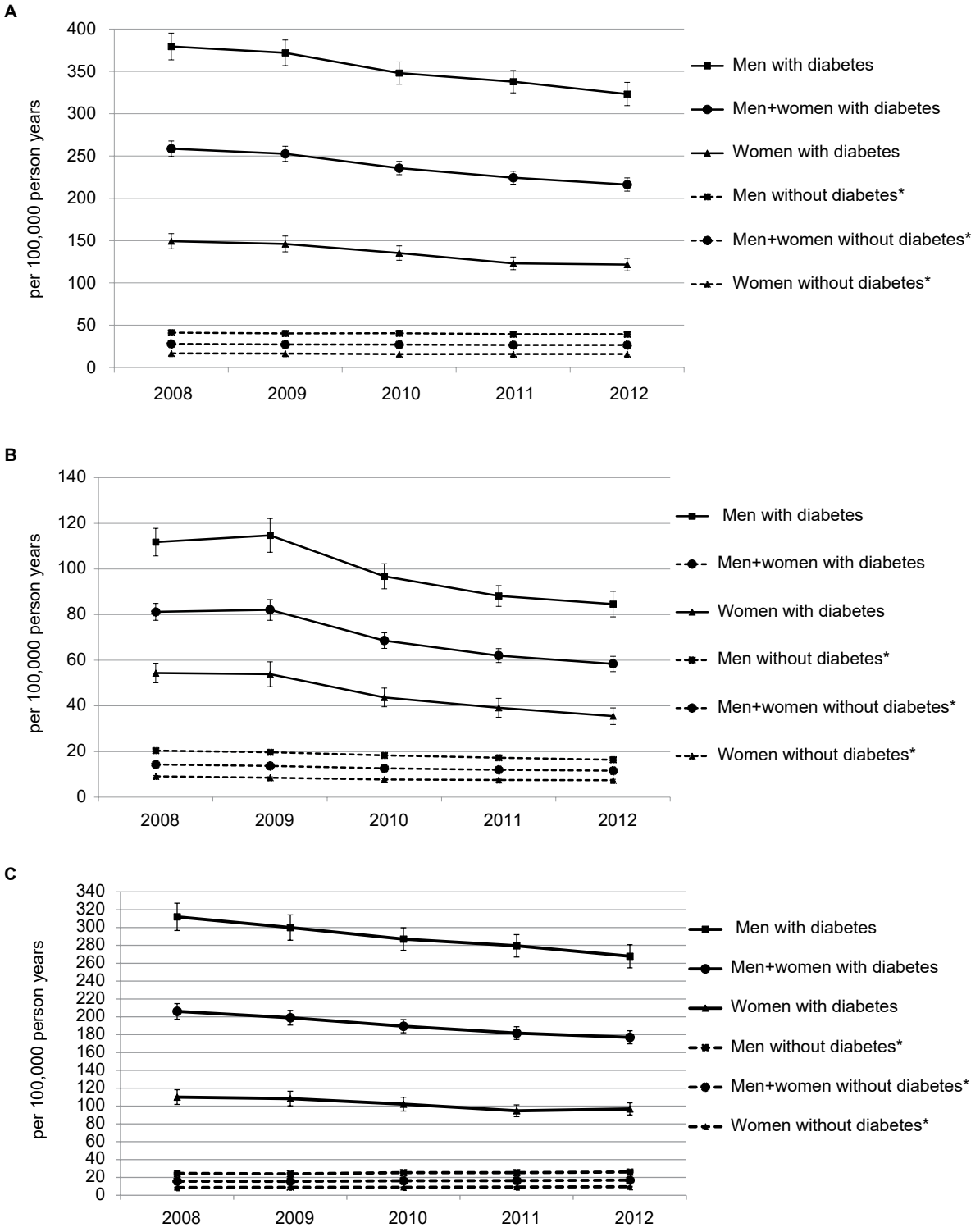

Figure 1 Time trend of age-sex-standardized amputation rate of (**A**) any amputation, (**B**) major amputation, and (**C**) minor amputation.
Note: *95% CI were relatively narrow and not distinct in figures.

Table 3 Relative risk (RR) of lower-extremity amputation in people with diabetes, compared with those without diabetes, adjusted for age, sex, and calendar year: results of the Poisson models

Independent variable	Total	Total		Total
		Men	Women	Diabetes
	RR	RR	RR	RR
Any amputation				
Year[a]	0.96 (0.95–0.98)*	0.97 (0.96–0.98)*	0.96 (0.94–0.98)*	0.96 (0.95–0.96)*
Diabetes (yes vs no)	6.95 (6.69–7.23)*	7.67 (7.35–8.00)*	5.75 (5.43–6.09)*	–
Sex (men vs women)	2.50 (2.41–2.59)*	–	–	2.47 (2.41–2.53)*
Age (years)[b]				
≥80	57.89 (49.37–67.88)*	46.17 (39.03–54.62)*	68.54 (53.23–88.26)*	11.74 (9.71–14.18)*
70–79	35.51 (30.31–41.61)	36.37 (30.82–42.92)*	32.82 (25.45–42.32)*	8.58 (7.10–10.36)*
60–69	24.58 (20.95–28.85)*	27.27 (23.09–32.21)*	17.37 (13.38–22.53)*	6.39 (5.28–7.72)*
50–59	15.31 (13.01–18.02)*	17.24 (14.57–20.40)*	10.42 (7.96–13.64)*	5.17 (4.27–6.27)*
40–49	5.62 (4.69–6.74)*	6.17 (5.13–7.43)*	4.39 (3.24–5.96)*	3.18 (2.61–3.89)
Major amputation				
Year[a]	0.92 (0.91–0.93)*	0.93 (0.92–0.94)*	0.91 (0.89–0.93)*	0.91 (0.90–0.92)*
Diabetes (yes vs no)	4.64 (4.45–4.83)*	4.94 (4.75–5.15)*	4.11 (3.86–4.38)*	–
Sex (men vs women)	2.21 (2.12–2.30)*	–	–	2.13 (2.06–2.20)*
Age (years)[b]				
≥80	110.04 (90.07–134.44)*	79.40 (65.98–95.55)*	146.77 (102.69–209.78)*	25.93 (17.78–37.81)*
70–79	58.23 (47.68–71.13)*	57.74 (48.08–69.34)*	58.97 (41.18–84.44)*	16.40 (11.24–23.91)*
60–69	37.55 (30.69–45.94)*	41.41 (34.45–49.78)*	27.31 (18.93–39.40)*	11.06 (7.58–16.14)*
50–59	19.94 (16.23–24.50)*	22.06 (18.30–26.59)*	14.44 (9.89–21.08)*	8.05 (5.5–11.77)*
40–49	6.58 (5.24–8.27)*	6.75 (5.49–8.30)*	6.15 (4.06–9.30)*	4.46 (3.01–6.61)*
Minor amputation				
Year[a]	0.98 (0.97–0.99)*	0.984 (0.971–0.997)*	0.981 (0.963–0.999)*	0.97 (0.96–0.98)*
Diabetes (yes vs no)	9.33 (8.96–9.71)*	10.14 (9.67–10.63)*	7.79 (7.34–8.28)*	–
Sex (men vs women)	2.74 (2.65–2.84)*	–	–	2.71 (2.65–2.77)*
Age (years)[b]				
≥80	42.5 (36.40–49.62)*	37.27 (31.09–44.68)*	45.00 (35.52–57.00)*	9.46 (8.00–11.19)*
70–79	28.89 (24.77–33.70)*	30.88 (25.83–36.92)*	24.57 (19.38–31.16)*	7.52 (6.36–8.89)*
60–69	20.33 (17.41–23.74)*	23.13 (19.33–27.67)*	13.75 (10.78–17.53)*	5.68 (4.80–6.72)*
50–59	13.66 (11.67–15.99)*	15.64 (13.05–18.76)*	9.08 (7.06–11.68)*	4.70 (3.96–5.56)*
40–49	5.31 (4.46–6.32)*	5.99 (4.91–7.31)*	3.89 (2.92–5.18)*	2.93 (2.45–3.50)*

Notes: [a]Relative risk per 1 year increment. [b]Reference category: <40 years. *Statistically significant difference, $p<0.05$.

ent definition of AR and some older populations with very low socioeconomic status in our study. However, the RRs from our study are somewhat lower in the international comparison with studies from Italy: RR for the entire study period 2001–2010 was 10.95 (95% CI 9.37–12.8)[4] and from France: RR in 2003 was 11.8 (95% CI 11.0–12.6).[14]

Major amputations are performed in cases of excessive tissue loss or sepsis[26] or if there are no further surgical or endovascular options for revascularization. They reduce the quality of life considerably and entail high mortality.[27,28]

In the present study, we observed a considerable reduction of 9% per year in major AR in the population with diabetes between 2008 and 2012, with an even greater reduction among women. This effect may be explained by improvements in the organization of diabetes foot care (diabetes management programs, national guidelines for prevention and treatment strategies for foot complications, nationwide establishment of certified diabetic foot clinics, and constitution of regional networks[29]). In the nondiabetic population, major AR likewise decreased by 6% per year in both sexes. Also, increased numbers of surgical and endovascular revascularizations may explain in part the positive time trend in the populations with and without diabetes.[30,31]

The positive time trend toward a significant reduction in major AR among people with diabetes observed in our nationwide study is in line with other epidemiologic studies.[2,4,17,32–34] Likewise, the RRs of major LEA, comparing people with and without diabetes, are comparable with the results from an earlier German study[3] and were lower compared with data from Italy (RR 6.36; 95% CI 5.6–7.23)[4] and Finland (RR 7.4; 95% CI 7.2–7.7).[17] Furthermore, we observed a significant reduction in RRs during the study period, which was also found in the studies by Trautner et al[2] and Ikonen et al,[17] but not in the study by Lombardo et al.[4]

	Men		Women	
No diabetes	Diabetes	No diabetes	Diabetes	No diabetes
RR	RR	RR	RR	RR
0.986 (0.969–1.003)	0.97 (0.96–0.97)*	0.988 (0.971–1.005)	0.94 (0.93–0.95)*	0.99 (0.96–1.01)
–	–	–	–	–
2.47 (2.35–2.59)	–	–	–	–
107.49 (93.25–123.91)*	10.00 (8.42–11.88)*	85.92 (74.83–98.66)*	13.21 (10.19–17.13)*	116.81 (93.22–146.37)*
42.83 (37.11–49.43)*	8.95 (7.54–10.63)*	48.17 (42.07–55.15)*	7.87 (6.07–10.21)*	33.91 (26.88–42.79)*
25.00 (21.58–28.96)*	7.05 (5.93–8.37)*	30.77 (26.82–35.31)*	4.73 (3.64–6.15)*	15.28 (11.95–19.54)*
11.67 (10.02–13.60)*	5.52 (4.64–6.57)*	14.34 (12.44–16.53)*	4.24 (3.25–5.54)*	6.83 (5.25–8.89)*
3.84 (3.21–4.58)*	3.22 (2.69–3.85)*	4.30 (3.64–5.06)*	3.15 (2.37–4.18)*	2.96 (2.19–4.00)*
0.94 (0.92–0.96)*	0.92 (0.91–0.93)*	0.95 (0.93–0.96)*	0.89 (0.88–0.91)*	0.94 (0.92–0.97)*
–	–	–	–	–
2.28 (2.15–2.42)*	–	–	–	–
161.35 (131.82–197.50)*	27.13 (17.81–41.32)*	109.78 (92.03–130.95)*	22.16 (13.87–35.39)*	221.28 (153.89–318.17)*
61.43 (50.11–75.31)*	22.12 (14.54–33.67)*	63.43 (53.35–75.43)*	11.17 (6.99–17.85)*	59.70 (41.24–86.43)*
37.67 (30.62–46.33)*	16.16 (10.61–24.6)*	43.57 (36.58–51.89)*	5.67 (3.53–9.09)*	26.68 (18.19–39.13)*
15.86 (12.80–19.66)*	11.16 (7.32–17.02)*	18.21 (15.20–21.81)*	4.79 (2.97–7.73)*	10.88 (7.27–16.30)*
5.03 (3.94–6.42)*	5.64 (3.66–8.69)*	5.08 (4.13–6.25)*	3.50 (2.11–5.81)*	4.94 (3.17–7.70)*
1.019 (1.001–1.037)*	0.98 (0.97–0.98)*	1.016 (0.996–1.037)	0.96 (0.95–0.98)*	1.025 (0.999–1.053)
–	–	–	–	–
2.73 (2.59–2.88)*	–	–	–	–
90.09 (78.49–103.40)*	8.19 (6.88–9.74)*	81.15 (69.51–94.73)*	10.85 (8.51–13.82)*	84.04 (68.29–103.41)*
37.58 (32.71–43.18)*	7.67 (6.45–9.12)*	44.68 (38.40–52.00)*	7.18 (5.63–9.15)*	26.01 (20.98–32.26)*
20.95 (18.15–24.19)*	6.06 (5.10–7.21)*	26.71 (22.87–31.19)*	4.51 (3.53–5.76)*	11.68 (9.27–14.71)*
10.52 (9.07–12.21)*	4.86 (4.08–5.78)*	13.37 (11.40–15.69)*	4.15 (3.23–5.32)*	5.69 (4.45–7.28)*
3.44 (2.89–4.10)*	2.89 (2.40–3.46)*	4.08 (3.39–4.91)*	3.10 (2.37–4.03)*	2.32 (1.73–3.11)*

Minor amputations are performed in order to remove necrotic tissues, prevent infections, create wounds that can heal under the conditions of modern wound management and offloading, and thus preserve as much of the foot as possible. They allow the person to ambulate with no need for prosthesis and do not affect health-related quality of life any more than conservative treatment.

In the present study, we found a reduction of 3% per year in minor AR among people with diabetes of both sexes, while among people without diabetes, the AR increased slightly – by 2% per year. Comparisons between our results and the findings from other studies were limited because only a few studies have analyzed minor AR considering one LEA per person, and, as mentioned above, study designs are hardly comparable.[4,32,35] The Italian study by Lombardo et al[4] showed an unchanged minor AR in the population with diabetes and a significant increase in minor LEA incidence in the population without diabetes; whereas a Spanish study[32] described a reduction in one minor LEA among people with diabetes. A study from Denmark showed a significant annual reduction of 9.8% in the population with diabetes and unchanged incidence rates in the population without diabetes during 1996–2011.[34]

Gender differences in minor LEAs were markedly pronounced: the risk among men for undergoing minor LEA was 2.7 times higher compared with women. This finding coincides with the results of other studies, which, however, were not able to fully elucidate the underlying reasons. Biologic factors seem to contribute to gender differences,[36,37] while health care-related and behavioral factors do not.[38,39]

In the present study, we observed a reduction in the RRs for minor LEA between the populations with and without diabetes during the study period that was quite similar across both sexes. Compared with the RRs found in a study from

Italy, the RRs calculated in the Poisson model from our study were lower (RR 9.33 (95% CI: 8.96–9.71) vs 19.37 (16.49–22.7).[4] Compared with RRs reported in a study from Denmark, those comparisons were different for men and women: the RR in our study was also lower for men (RR men 10.14 (95% CI 9.67–10.63) vs 14.7 (10.5–20.4), but well in line among women: RR 7.79 (7.34–8.28) vs 7.5 (5.2–10.9).[34]

Some limitations of this study should be considered. First, the study population included only people with SHI, so the privately insured (11% of the German population[40]), which is somewhat younger and healthier than the SHI population,[41] could not be considered. Furthermore, persons insured by the included SHIs may differ from those of other companies.[41] Second, regarding selection of the person-time of all insured individuals, we used an algorithm that excluded individuals with gaps in SHI of more than 30 days in two consecutive quarters. A previous study demonstrated that people who change their insurance company are younger, better educated, and have a lower prevalence of diabetes and cardiovascular disease.[42] As a consequence, our study population was somewhat older than the general German population, which was particularly true for women (proportion in 2010: 5.4% women over 80 years in our data set vs 3.5% women over 80 years in the whole of Germany; 2.1% men over 80 years in our data set vs 1.7% men over 80 years in the whole of Germany). However, the prevalence of diabetes in our study was well in line with recently published nationwide data.[43,44] Third, there may be some misclassification concerning the "population at risk," referring to the population with diabetes. This may be due to undiagnosed diabetes or due to prescription of antihyperglycemic drugs for people with impaired glucose regulation. However, we assume that the latter in particular should be rare. Moreover, in our study, based on the administrative data for the identification of people with diabetes, we have used one established algorithm, which has already been applied successfully by other studies.[15,45] Furthermore, within our study, the characteristics of the population are similar to other German data, for example, the relation between insured persons with a diagnosis of diabetes with and without pharmacotherapy is in line with other studies from Germany.[44,46–48] Fourth, unfortunately, with our data set, we were not able to estimate the AR of LEA stratified by type 1 and type 2 diabetes. Fifth, only the first amputation per patient and year, and not the all-time first amputation per patient, could be analyzed since we were not able to overlook whether amputations occurred before 2008, in order to estimate the first ever amputation. This might create a bias in the incidence estimations between the populations with and without diabetes. Sixth, adjustment for comorbidity is an important prognostic factor in risk adjustment modeling for different outcomes.[49] However, in our study, due to data protection requirements during the process of data extraction, the final study data set lacks related information on individual comorbidities. Thus, we could not adjust our estimates for further potential confounders such as coronary heart disease, cerebrovascular disease, or peripheral arterial disease. These diseases are well-known risk factors for a high incidence of LEA.[50–53] The lifetime prevalence of coronary heart disease and stroke among adults aged 40–79 years was 9.3% and 2.9%, respectively, according to the nationwide German Health Interview and Examination Survey for Adults (DEGS1) in 2008–2011.[51,53] However, no significant change over time between 1998 and 2010 of the prevalence of these cardiovascular diseases was observed,[51,53] potentially indicating that these comorbidities have no impact on the time trend of LEA. Further important factors that could also influence the AR, such as lifestyle variables, are not available in SHI data. However, looking for possible explanatory factors was not the aim of our study. Our aim was to describe the LEA risk and RR according to the St Vincent goals using a data source that enables us to analyze more than 30 million people in Germany, which is in line with several large epidemiological studies.[4,14,22] Finally, there were strong multiple interactions between diabetes, age, and sex, which might provoke biased results in stratified Poisson models. However, the results of the latter with regard to time trend were largely in line with those based on age-sex-standardized AR.

This study has a number of strengths. First, this is of the largest studies to cover more than 40% of the German population. Second, we defined the population with diabetes using a uniform algorithm, including people who are not receiving antihyperglycemic treatment.[15] This is a compelling prerequisite for a valid estimation of AR in the populations with and without diabetes. Other studies that did not use this tool had to use estimated diabetes prevalence.[2,12,32] Third, our study population is a dynamic cohort, including patients with new-onset diabetes mellitus during the study period. Finally, we were able to report the AR and time trend stratified by amputation level.

In conclusion, the present study is an analysis of AR, RR, and corresponding time trends in the largest nationwide population of Germany ever studied. The AR remained higher in the diabetic compared with the nondiabetic population. During the study period, we found a significant continuous reduction in the major and minor ARs among patients with diabetes and reduced major AR among those without diabe-

tes. In contrast, minor AR slightly increased among people without diabetes. During the study period, RR for both major and minor LEA in the diabetic compared to the nondiabetic population decreased significantly. Our findings point to the need for continuous national monitoring of LEAs.

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Author contributions

HC made substantial contributions to the design of the study, conducted the analysis and interpreted the data, and drafted the manuscript. MN made substantial contributions to the conception and design of the study, researched data, and contributed to the concept, design, and drafting of the manuscript. BH and WA researched data, contributed to the data interpretation, and critically commented on the manuscript for scientific content. FH, SM, GR, and TK contributed substantially to the data interpretation and discussion. HF, CG, WU, BW, and AW prepared and extracted data and contributed substantially to the concept, design, and data interpretation. IS and AI contributed substantially to the conception and design of the study, acquisition of data, data interpretation, and discussion. All authors contributed toward data analysis, critically revised the manuscript for important intellectual content, approved the final manuscript, and agreed to be accountable for all aspects of the work.

AI is the guarantor of this work and, as such, has full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Disclosure

The authors report no conflicts of interest in this work.

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ARTICLE

Decreasing rates of major lower-extremity amputation in people with diabetes but not in those without: a nationwide study in Belgium

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Abstract

Aims/hypothesis The reduction of major lower-extremity amputations (LEAs) is one of the main goals in diabetes care. Our aim was to estimate annual LEA rates in individuals with and without diabetes in Belgium, and corresponding time trends.

Methods Data for 2009–2013 were provided by the Belgian national health insurance funds, covering more than 99% of the Belgian population (about 11 million people). We estimated the age–sex standardised annual amputation rate (first per year) in the populations with and without diabetes for major and minor LEAs, and the corresponding relative risks. To test for time trends, Poisson regression models were fitted.

Results A total of 5438 individuals (52.1% with diabetes) underwent a major LEA, 2884 people with above- and 3070 with below-the-knee major amputations. A significant decline in the major amputation rate was observed in people with diabetes (2009: 42.3; 2013: 29.9 per 100,000 person-years, 8% annual reduction, $p < 0.001$), which was particularly evident for major amputations above the knee. The annual major amputation rate remained stable in individuals without diabetes (2009: 6.1 per 100,000 person-years; 2013: 6.0 per 100,000 person-years, $p = 0.324$) and thus the relative risk reduced from 6.9 to 5.0 ($p < 0.001$). A significant but weaker decrease was observed for minor amputation in individuals with and without diabetes (5% and 3% annual reduction, respectively, $p < 0.001$).

Conclusions/interpretation In this nationwide study, the risk of undergoing a major LEA in Belgium gradually declined for individuals with diabetes between 2009 and 2013. However, continued efforts should be made to further reduce the number of unnecessary amputations.

Keywords Amputation rate · Diabetes · Major lower-extremity amputation · Minor lower-extremity amputation · National health insurance funds

Abbreviations

ARd	Amputation rate for the estimated population with diabetes
ARn	Amputation rate for the population without diabetes
ESP	European Standard Population
IMA/AIM	InterMutualistisch Agentschap/Agence InterMutualiste
LEA	Lower-extremity amputations

Heiner Claessen and Herve Avalosse are joint first authors. Kristien Van Acker and Andrea Icks are joint senior authors.

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Introduction

Lower-extremity amputations (LEAs) have a huge impact on individuals and also on society [1, 2]. Practical issues such as reduced mobility, pain, hospitalisation, revalidation, disability and unemployment, a changed self-image and difficulties with activities of daily living lead to reduced quality of life for the person affected and their relatives. There are also considerable financial consequences—especially with a major amputation [1].

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Research in context

What is already known about this subject?

- Many reports have already demonstrated that a substantial decrease in the incidence of major amputations, as well as a decrease in the total incidence of amputations, in people with diabetes, is feasible after the implementation of multidisciplinary and trans-sectoral programmes for diabetic foot ulcer care and prevention
- Data on lower-extremity amputations (LEAs) are available from several countries in different continents; however, the number of studies comparing incidence in populations with and without diabetes is still limited

What is the key question?

- How did the annual amputation rate in people with and without diabetes in Belgium change during the period 2009–2013?

What are the new findings?

- We found a strong decline in the major amputation rate in people with diabetes, but not in people without diabetes. The relative risk comparing people with and without diabetes decreased but remained high
- The decline in the amputation rate in those with diabetes was particularly prominent for major amputations above the knee
- We also observed a weaker but still significant decrease in the amputation rate for minor LEAs in people with and without diabetes

How might this impact on clinical practice in the foreseeable future?

- Continuous efforts should be made to further reduce the number of unnecessary amputations. Nationwide coverage with specialised centres for diabetic foot ulcer care and prevention should be discussed

A substantial proportion of LEAs, particularly in people with diabetes, are thought to be preventable via the provision of appropriate healthcare. Many reports have already demonstrated that a substantial decrease in the incidence of major amputations, as well as a decrease in the total incidence of amputations, in people with diabetes, is feasible after implementation of a multidisciplinary programme for the prevention and treatment of diabetic foot ulcers, including earlier and more frequent use of revascularisation procedures [3, 4].

Such a programme to prevent and treat the diabetic foot ulcer has been introduced in Belgium. In 1989, the first multidisciplinary foot clinic was established at the University of Antwerp, followed by a gradual process of decentralisation. In the early 1990s, national campaigns were organised at the primary care level. In 2005, a national diabetic foot care programme was established involving recognised diabetic foot clinics. The number of diabetic foot clinics recognised by the Belgian Ministry of Health increased from 21 in 2008 to 34 in 2014. In order to maintain this recognition, diabetic foot clinics are required to participate in a quality-improvement initiative (Initiative for Quality Improvement and Epidemiology in Multidisciplinary Diabetic Foot Clinics [IQED-Foot]). The activities within this initiative can be summarised as follows: evaluating quality of care based on repeated audits; improving quality of care by providing individual feedback with anonymous benchmarking; and organising informative meetings to add to scientific knowledge on the presentation and management of and outcomes in people with diabetic foot ulcers [5, 6].

Information on the incidence of LEAs that is accurate, up-to-date and comparable is essential to guide and monitor interventions aimed at LEA prevention [3, 7]. Data on LEAs are available from several countries in different continents. However, the number of studies that have estimated the risk of amputation among the population ‘at risk’ (i.e. in the populations with and without diabetes, respectively) remains limited [8–15]. In order to evaluate which changes are specific for the diabetic situation, knowledge is needed both of the incidence of LEAs in the non-diabetic population and of RRs.

Hence, the aim of this study was to analyse the annual major as well as minor LEA rates in people with and without diabetes in Belgium, and to evaluate whether these changed during the period 2009–2013. To the best of our knowledge, this paper is the first to evaluate the LEA rate in Belgium based on a nationwide dataset.

Methods

Study population and data assessment The study population comprised almost the entire Belgian population (>99%). We used data from the Belgian national health insurance funds, provided by the InterMutualistisch Agentschap/Agence

InterMutualiste (IMA/AIM), for all individuals who were insured for at least one day in Belgium between 1 January 2009 and 31 December 2013. The following information was available for all insured people: year of birth (based on 5 year intervals), sex, diagnosis of diabetes and amputation (including level of amputation).

Individuals were classified as 'with diabetes' if they met at least one of the following criteria: (1) inclusion in a diabetes care programme; (2) treatment with diabetes-specific medication; and/or (3) registration of repeated HbA_{1c} measurements. Inclusion in one of the three diabetes care programmes in Belgium could be defined by ownership of a 'diabetes passport', inclusion in a diabetes care plan, inclusion in a diabetes meeting or patient reimbursement of glucose meters, strips and lancets. Treatment with diabetes-specific medication was defined as intake of glucose-lowering medication based on the World Health Organization classification within one calendar year (ATC codes A10A and A10B, at least 90 defined daily doses per year). Registration for repeated measurement of HbA_{1c} levels was considered if at least three HbA_{1c} measurements had been carried out over two consecutive calendar years. Hospitalised individuals who had drugs issued only by the hospital pharmacy were excluded because this could be related to transient hyperglycaemia during acute illness in people otherwise not suffering from diabetes. Likewise, gestational diabetes, which was ascertained when a woman received glucose-lowering medication only during pregnancy, was excluded.

LEAs were classified according to the official nomenclature codes (provided by the IMA/AIM). We further differentiated between major amputation (any amputation above the ankle) and minor amputation (below the ankle); major LEAs were additionally subdivided into major below-the-knee amputation and major above-the-knee LEA (knee disarticulation or proximal).

These data were anonymised, aggregated and analysed by blinded investigators. Therefore, neither ethical approval nor individual written consent from participants was required.

Statistical analysis We conducted all analyses for the entire population, and stratified by sex. They were performed for major LEAs, major LEAs above and below the knee, and minor LEAs as outcomes. Furthermore, all LEAs were additionally analysed.

We computed diabetes prevalence and assessed the time trend using the χ^2 test. For each outcome, we estimated the amputation rate for each calendar year as follows: the number of people with an outcome occurring within this year as numerator was divided by the number of insured people in the respective year as denominator. Therefore, the amputation rate could count one person several times in different calendar years if multiple outcomes occurred in different years (e.g. major amputation of the left leg in 2009, major amputation of the right leg in 2010). A major LEA was also counted for analysis if a person had previously undergone a minor LEA, even if this was in the same calendar year.

We directly computed age–sex standardised amputation rates and, for the sex-specific analyses, age–standardised amputation rates using 0–39, 40–49, 50–59, 60–69, 70–79, 80+ years as age strata (standard population: Belgian population 2011) for each calendar year for the estimated population with diabetes (amputation rate for the estimated population with diabetes [ARd]) and the population without diabetes (amputation rate for the population without diabetes [ARn]), respectively. For international comparisons, we also standardised the major amputation rate for the European Standard Population (ESP) 2013 as sensitivity analysis [16]. Furthermore, we calculated RR in order to divide the amputation rates in individuals with diabetes by those in people without diabetes (ARd/ARn).

In order to test for time trends, we fitted separate Poisson regression models for the population with and without diabetes using year of outcome (difference from the first year 2009 as an ordinal variable), age (groups as described above) and sex as independent variables. Additionally, we calculated Poisson regression models for the entire population. In these, an additional variable for the presence of diabetes ('yes' vs 'no') was included, as well as an interaction term 'presence of diabetes' with 'years since 2009'. All models were adjusted for over-dispersion using a dispersion parameter.

All analyses were conducted using the Statistical Analysis System (SAS for Windows 7, Release 9.4 TS1M2, SAS Institute, Cary, NC, USA).

Results

Study population The description of the background population, numbers and age–sex standardised rates of major amputation (any major, major above the knee, major below the knee) and minor amputation, as well as corresponding RRs, are shown for each calendar year in Table 1 and Figs 1, 2, 3 and 4. The results of the time trend for the major and minor amputation rates in the population with diabetes from the fully adjusted Poisson models are presented in Table 2. The total study population comprised approximately 11 million insurants (2009: 10,877,318; 2013: 11,165,978). Diabetes prevalence rose from 6.2% in 2009 to 8.0% in 2013 (χ^2 test $p < 0.001$), with somewhat higher values in the female population.

Major amputation We identified 5438 individuals with any major amputation in the period 2009–2013, of whom almost two-thirds were male (65%). More than half (52%) of all individuals with an LEA were people with diabetes. The mean age of all amputees (71 years) remained nearly stable over the period. However, women were markedly older than men at the time of major amputation (75 vs 70 years) and the people with diabetes were older compared with people without diabetes

Table 1 Baseline characteristics of major and minor amputations, Belgium, 2009–2013

Population/ calendar year	Diabetes				No diabetes				
	Number of people with amputation	Mean age[a] (years)	Number of total population	ARd[b]	Number of people with amputation	Mean age[a] (years)	Number of total population	ARn[b]	RR[c]
All major amputations									
Total population									
2009	618	72.4	678,655	42.3	554	69.5	10,198,663	6.1	6.9
2010	631	71.9	738,256	43.8	549	69.9	10,226,043	6.1	7.2
2011	590	71.9	793,883	37.6	578	69.9	10,255,320	6.4	5.9
2012	569	71.6	846,796	34.5	537	69.3	10,271,802	5.9	5.8
2013	599	71.9	896,126	29.9	542	69.7	10,269,852	6.0	5.0
Male population									
2009	404	71.0	326,803	59.1	347	66.2	5,021,923	8.7	6.8
2010	400	70.5	354,104	60.8	336	66.4	5,038,345	8.5	7.2
2011	399	70.0	379,168	57.6	360	67.7	5,056,551	9.1	6.3
2012	385	69.9	402,725	52.8	341	66.9	5,067,837	8.5	6.2
2013	411	70.8	424,291	44.2	351	67.5	5,068,800	8.8	5.0
Female population									
2009	214	75.1	351,852	28.1	207	75.1	5,176,740	4.0	7.1
2010	231	74.3	384,152	28.7	213	75.3	5,187,698	4.1	7.1
2011	191	75.7	414,715	19.3	218	73.7	5,198,769	4.2	4.6
2012	184	75.3	444,071	18	196	73.5	5,203,965	3.8	4.8
2013	188	74.3	471,835	17.7	191	73.8	5,201,052	3.7	4.8
Major amputations above the knee									
Total population									
2009	281	73.8	678,655	17.6	323	71.2	10,198,663	3.6	4.9
2010	285	74.4	738,256	16.6	300	72.3	10,226,043	3.4	4.9
2011	274	73.8	793,883	17.8	329	71.7	10,255,320	3.7	4.8
2012	259	74.4	846,796	12.6	356	71.0	10,271,802	4.0	3.2
2013	247	73.3	896,126	11.4	328	71.1	10,269,852	3.6	3.2
Male population									
2009	173	72.6	326,803	22.7	202	67.8	5,021,923	5.2	4.4
2010	164	72.7	354,104	20.5	173	69.0	5,038,345	4.4	4.6
2011	166	71.9	379,168	25.7	202	69.2	5,056,551	5.2	5.0
2012	161	72.1	402,725	17.6	221	68.7	5,067,837	5.6	3.1
2013	159	71.5	424,291	16.0	209	67.8	5,068,800	5.3	3.1
Female population									
2009	108	75.7	351,852	13.9	121	76.9	5,176,740	2.3	6.1
2010	121	76.7	384,152	13.3	127	76.6	5,187,698	2.4	5.5
2011	108	76.8	414,715	10.5	127	75.8	5,198,769	2.4	4.3
2012	98	78.2	444,071	8.4	135	74.8	5,203,965	2.6	3.2
2013	88	76.6	471,835	7.6	119	76.9	5,201,052	2.3	3.3
Major amputations below the knee									
Total population									
2009	385	71.3	678,655	27.6	271	67.2	10,198,663	3.0	9.3
2010	399	69.9	738,256	30.2	284	66.9	10,226,043	3.1	9.7
2011	360	70.2	793,883	22.1	281	67.9	10,255,320	3.1	7.2
2012	342	69.5	846,796	23.6	224	66.7	10,271,802	2.5	9.6
2013	393	70.6	896,126	20.5	256	68.0	10,269,852	2.8	7.3

Table 1 (continued)

Population/ calendar year	Diabetes				No diabetes				
	Number of people with amputation	Mean age[a] (years)	Number of total population	ARd[b]	Number of people with amputation	Mean age[a] (years)	Number of total population	ARn[b]	RR[c]
Male population									
2009	262	69.9	326,803	40.2	174	64.0	5,021,923	4.2	9.5
2010	271	69.3	354,104	44.4	185	63.8	5,038,345	4.6	9.7
2011	264	68.9	379,168	35.3	180	65.9	5,056,551	4.5	7.9
2012	251	68.4	402,725	38.3	151	64.9	5,067,837	3.7	10.2
2013	282	70.0	424,291	31.3	173	67.3	5,068,800	4.3	7.3
Female population									
2009	123	74.2	351,852	16.5	97	72.9	5,176,740	1.9	8.9
2010	128	71.1	384,152	17.5	99	72.9	5,187,698	1.9	9.3
2011	96	73.8	414,715	10.4	101	71.4	5,198,769	1.9	5.4
2012	91	72.4	444,071	9.9	73	70.4	5,203,965	1.4	7.0
2013	111	72.0	471,835	11.2	83	69.4	5,201,052	1.6	7.1
Minor amputations									
Total population									
2009	1232	70.3	678,655	91.3	772	68.9	10,198,663	8.5	10.7
2010	1242	70.9	738,256	85.0	740	68.4	10,226,043	8.1	10.5
2011	1223	70.0	793,883	82.5	746	67.0	10,255,320	8.2	10.1
2012	1299	70.7	846,796	75.7	695	67.7	10,271,802	7.6	9.9
2013	1325	70.9	896,126	77.1	704	67.6	10,269,852	7.7	10.1
Male population									
2009	860	68.6	326,803	139.0	423	66.5	5,021,923	10.8	12.9
2010	838	69.3	354,104	125.9	397	65.5	5,038,345	10.1	12.5
2011	860	68.7	379,168	127.2	407	65.2	5,056,551	10.3	12.4
2012	903	69.6	402,725	114.9	373	66.0	5,067,837	9.5	12.1
2013	935	69.8	424,291	119.0	367	65.4	5,068,800	9.2	13
Female population									
2009	372	74.1	351,852	47.9	349	71.7	5,176,740	6.7	7.2
2010	404	74.3	384,152	48.5	343	71.7	5,187,698	6.6	7.4
2011	363	72.9	414,715	42.1	339	69.1	5,198,769	6.5	6.5
2012	396	73.3	444,071	41.1	322	69.8	5,203,965	6.2	6.6
2013	390	73.7	471,835	40.1	337	70.0	5,201,052	6.4	6.2

[a] Age at time of first amputation

[b] Amputation rate per 100,000 person-years in the population with diabetes and without diabetes, standardised to the Belgian population 2011

[c] RR comparing amputation rates in the population with and without diabetes (ARd/ARn)

(72 vs 70 years). These numbers remained nearly stable in the period 2009–2013. We identified 3070 individuals undergoing major amputation below the knee (men: 69%; diabetes: 59%) and 2884 individuals undergoing a major amputation above the knee (men: 61%; diabetes: 45%).

Throughout the observation period, the major amputation risk was more than six times higher in people with diabetes compared with individuals without diabetes (RR 6.122; 95% CI 5.776, 6.489) (Table 2). This difference was particularly evident when only amputations below the knee were considered (RR 8.049; 95% CI 7.533, 8.602) but also remained significantly increased for amputations above the knee (RR 4.747; 95% CI 4.441, 5.074).

We observed a significant decrease in the rate of any major amputation in the population with diabetes, from 42.3 per 100,000 person-years in 2009 to 29.9 in 2013 (Table 1, Fig. 1), with an annual reduction of 8% (RR per calendar year 0.920; 95% CI 0.909, 0.931) (Table 2). In contrast, no decline was observed in the population without diabetes (2009: 6.1; 2013: 6.0 [Table 1]; RR per calendar year 0.991; 95% CI 0.974, 1.009 [Table 2]). As a result, the RR comparing any major amputation rate in the population with and without

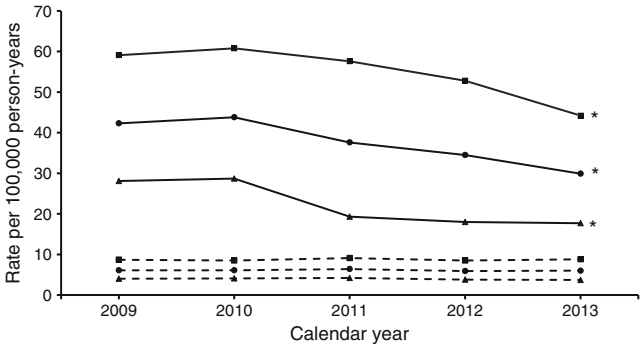

Fig. 1 Time trend of age- and sex-standardised major amputation rate. Solid lines, people with diabetes; dashed lines, people without diabetes; circles, men and women; squares, men; triangles, women. *$p < 0.05$ for time trend (Poisson model)

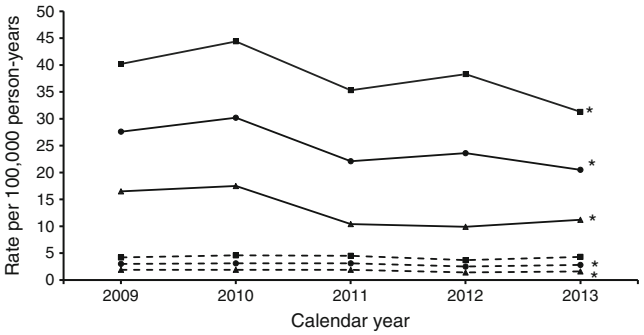

Fig. 3 Time trend of age- and sex-standardised major below-the-knee amputation rate. Solid lines, people with diabetes; dashed lines, people without diabetes; circles, men and women; squares, men; triangles, women. *$p < 0.05$ for time trend (Poisson model)

diabetes decreased significantly by 7% per year (RR interaction diabetes × calendar year: 0.927; 95% CI 0.905, 0.949) (Table 2). The decrease in any major amputation rate in the population with diabetes was more prominent when considering solely major amputations above the knee (2009: 17.6; 2013: 11.4) (Table 1, Fig. 2) with an annual decline of 10% (RR per calendar year 0.902; 95% CI 0.888, 0.917) (Table 2). With regard to major amputations below the knee, we observed a weaker but still significant decrease (2009: 27.6; 2013: 20.5) (Table 1, Fig. 3) with an annual reduction of 7% (RR per calendar year 0.926; 95% CI 0.913, 0.938) (Table 2).

In the population without diabetes, the major above-the-knee amputation rate remained constant (2009: 3.6; 2013: 3.6) (Fig. 2) whereas there was a significant decrease in major below-the-knee amputations, with an annual reduction of 4% (RR 0.964; 95% CI 0.944, 0.984) (Table 2, Fig. 3). Thus, the reduction in the RR comparing the rates among people with and without diabetes was particularly strong when only amputations above the knee were taken into account (RR 0.886; 95% CI 0.862, 0.910) but also remained significant considering only amputations below the knee (RR 0.960; 95% CI 0.934, 0.986).

The major amputation rates were more than twice as high in men compared with women and strongly increased with age, which was true among people with, as well as those without, diabetes (Table 2). The reduction in the major amputation rate was more pronounced among women in all subgroups, while the change in RR was comparable in both sexes. The major amputation rate did not materially alter after standardisation for the ESP 2013 (electronic supplementary material [ESM] Table 1).

Minor amputation We identified 8811 people undergoing minor amputation (men: 62.8%; diabetes: 60.7%) (Table 1 and Fig. 4). We observed a significant decrease in the minor amputation rate in the population with diabetes from 91.3 per 100,000 person-years in 2009 to 77.1 in 2013 (5% annual reduction; RR per calendar year 0.954; 95% CI 0.945, 0.962; Table 2, Fig. 4). Likewise, a consistent decrease was seen among people without diabetes (2009: 8.5 per 100,000 person-years; 2013: 7.7; 3% annual reduction; RR per calendar year 0.973; 95% CI 0.959, 0.988), which was significant in men but not in women. Over the

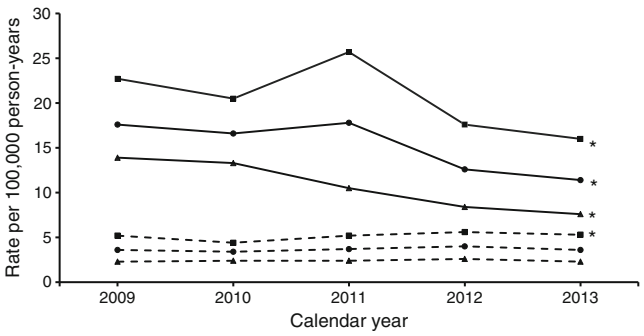

Fig. 2 Time trend of age- and sex-standardised major above-the-knee amputation rate. Solid lines, people with diabetes; dashed lines, people without diabetes; circles, men and women; squares, men; triangles, women. *$p < 0.05$ for time trend (Poisson model)

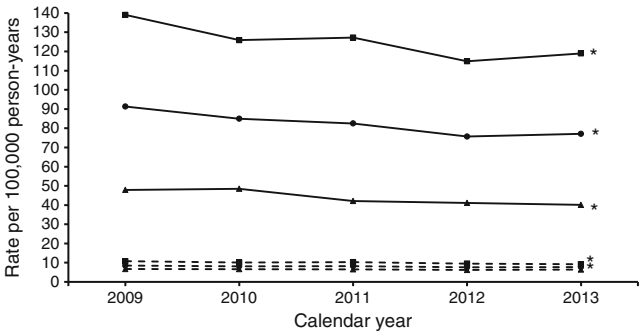

Fig. 4 Time trend of age- and sex-standardised minor amputation rate. Solid lines, people with diabetes; dashed lines, people without diabetes; circles, men and women; squares, men; triangles, women. *$p < 0.05$ for time trend (Poisson model)

Table 2 Results of Poisson models: relative risks for amputation, Belgium 2009–2013

Variables	RR (95% CI)		
	Total population	Men	Women
Any major amputation			
Model 1a (diabetes)			
Calendar year	0.920 (0.909, 0.931)*	0.933 (0.920, 0.946)*	0.894 (0.877, 0.911)*
Male vs female	2.258 (2.177, 2.342)*	–	–
Age (years)[a]			
≥80	18.824 (15.162, 23.369)*	10.618 (8.424, 13.383)*	52.671 (33.593, 82.583)*
70–79	13.688 (11.027, 16.991)*	8.418 (6.686, 10.598)*	34.452 (21.958, 54.056)*
60–69	9.308 (7.493, 11.563)*	6.100 (4.843, 7.682)*	19.087 (12.132, 30.029)*
50–59	6.759 (5.426, 8.419)*	4.161 (3.293, 5.258)*	16.967 (10.748, 26.786)*
40–49	3.39 (2.673, 4.299)*	1.857 (1.432, 2.409)*	10.543 (6.569, 16.924)*
Model 1b (no diabetes)			
Calendar year	0.991 (0.974, 1.009)	1.001 (0.981, 1.022)	0.975 (0.951, 1.000)
Male vs female	2.242 (2.130, 2.360)*	–	–
Age (years)[a]			
≥80	71.017 (63.367, 79.591)*	59.204 (51.699, 67.799)*	81.253 (68.314, 96.642)*
70–79	38.504 (34.279, 43.249)*	42.539 (37.225, 48.612)*	31.441 (26.184, 37.752)*
60–69	18.428 (16.345, 20.776)*	22.005 (19.210, 25.207)*	11.759 (9.650, 14.328)*
50–59	9.538 (8.417, 10.808)*	10.273 (8.908, 11.847)*	8.052 (6.589, 9.840)*
40–49	3.604 (3.111, 4.176)*	4.098 (3.477, 4.830)*	2.579 (2.002, 3.321)*
Model 2 (both diabetes and no diabetes combined)			
Calendar year	0.991 (0.974, 1.008)	1.001 (0.980, 1.021)	0.975 (0.950, 1.002)
Diabetes (yes vs no)	6.122 (5.776, 6.489)*	6.336 (5.908, 6.796)*	5.708 (5.211, 6.253)*
Male vs female	2.252 (2.174, 2.336)*	–	–
Age (years)[a]			
≥80	53.132 (47.956, 59.028)*	44.619 (39.564, 50.494)*	65.211 (55.092, 77.842)*
70–79	33.552 (30.274, 37.286)*	33.634 (29.871, 38.007)*	33.117 (27.880, 39.655)*
60–69	19.63 (17.692, 21.839)*	21.278 (18.890, 24.052)*	15.080 (12.608, 18.170)*
50–59	11.378 (10.218, 12.699)*	11.572 (10.231, 13.130)*	10.734 (8.933, 12.986)*
40–49	4.192 (3.692, 4.764)*	4.266 (3.690, 4.939)*	4.002 (3.214, 4.995)*
Diabetes × calendar year	0.927 (0.905, 0.949)*	0.932 (0.906, 0.958)*	0.916 (0.882, 0.951)*
Major amputation above the knee			
Model 1a (diabetes)			
Calendar year	0.902 (0.888, 0.917)*	0.914 (0.896, 0.933)*	0.883 (0.863, 0.905)*
Male vs female	1.869 (1.783, 1.959)*	–	–
Age (years)[a]			
≥80	39.803 (27.408, 57.803)*	23.887 (15.173, 37.606)*	74.895 (40.68, 137.884)*
70–79	24.376 (16.781, 35.41)*	15.969 (10.15, 25.125)*	41.965 (22.769, 77.345)*
60–69	14.385 (9.89, 20.922)*	10.324 (6.557, 16.256)*	19.257 (10.403, 35.644)*
50–59	9.124 (6.247, 13.326)*	6.197 (3.916, 9.805)*	14.368 (7.709, 26.779)*
40–49	4.681 (3.131, 6.998)*	2.342 (1.417, 3.87)*	11.422 (6.02, 21.671)*
Model 1b (no diabetes)			
Calendar year	1.018 (0.998, 1.039)	1.029 (1.004, 1.054)*	1.003 (0.974, 1.032)
Male vs female	2.155 (2.032, 2.285)*	–	–
Age (years)[a]			
≥80	110.327 (94.446, 128.879)*	93.062 (76.83, 112.723)*	120.183 (95.767, 150.824)*
70–79	61.266 (52.349, 71.702)*	69.182 (57.253, 83.596)*	48.389 (38.246, 61.223)*
60–69	27.25 (23.182, 32.031)*	33.959 (28.021, 41.155)*	16.077 (12.499, 20.681)*

Table 2 (continued)

Variables	RR (95% CI)		
	Total population	Men	Women
50–59	12.64 (10.677, 14.965)*	14.959 (12.246, 18.273)*	8.535 (6.555, 11.113)*
40–49	4.55 (3.741, 5.533)*	5.241 (4.168, 6.591)*	3.282 (2.396, 4.497)*
Model 2 (both diabetes and no diabetes combined)			
Calendar year	1.018 (1.000, 1.037)	1.028 (1.005, 1.052)*	1.003 (0.976, 1.031)
Diabetes (yes vs no)	4.747 (4.441, 5.074)*	4.603 (4.233, 5.004)*	4.893 (4.433, 5.400)*
Male vs female	2.024 (1.946, 2.105)*	–	–
Age (years)[a]			
≥80	95.278 (83.499, 109.273)*	84.078 (71.588, 99.458)*	104.238 (85.069, 129.41)*
70–79	55.2 (48.34, 63.351)*	59.146 (50.414, 69.898)*	49.112 (39.935, 61.166)*
60–69	28.1 (24.56, 32.308)*	33.297 (28.351, 39.388)*	18.763 (15.119, 23.553)*
50–59	14.174 (12.324, 16.373)*	16.083 (13.617, 19.121)*	10.681 (8.521, 13.525)*
40–49	5.129 (4.36, 6.046)*	5.321 (4.382, 6.483)*	4.788 (3.692, 6.239)*
Diabetes × calendar year	0.886 (0.862, 0.910)*	0.889 (0.86, 0.92)*	0.881 (0.846, 0.918)*
Major amputation below the knee			
Model 1a (diabetes)			
Calendar year	0.926 (0.913, 0.938)*	0.941 (0.927, 0.956)*	0.889 (0.867, 0.911)*
Male vs female	2.649 (2.541, 2.762)*	–	–
Age (years)[a]			
≥80	12.335 (9.902, 15.367)*	7.638 (6.065, 9.619)*	35.56 (21.074, 60.004)*
70–79	11.139 (8.949, 13.864)*	7.057 (5.615, 8.869)*	31.227 (18.506, 52.692)*
60–69	8.525 (6.845, 10.616)*	5.647 (4.493, 7.097)*	20.585 (12.17, 34.817)*
50–59	6.427 (5.147, 8.026)*	3.99 (3.164, 5.031)*	19.349 (11.403, 32.83)*
40–49	3.042 (2.388, 3.875)*	1.795 (1.386, 2.324)*	9.989 (5.758, 17.328)*
Model 1b (no diabetes)			
Calendar year	0.964 (0.944, 0.984)*	0.977 (0.952, 1.002)	0.940 (0.910, 0.971)*
Male vs female	2.463 (2.315, 2.621)*	–	–
Age (years)[a]			
≥80	48.973 (43.346, 55.332)*	41.896 (36.022, 48.727)*	56.046 (46.219, 67.964)*
70–79	26.496 (23.376, 30.033)*	29.954 (25.832, 34.734)*	19.987 (16.21, 24.644)*
60–69	14.072 (12.373, 16.004)*	16.215 (13.947, 18.852)*	9.597 (7.682, 11.989)*
50–59	8.469 (7.422, 9.664)*	8.226 (7.025, 9.632)*	8.97 (7.235, 11.122)*
40–49	3.331 (2.851, 3.893)*	3.805 (3.182, 4.551)*	2.229 (1.671, 2.973)*
Model 2 (both diabetes and no diabetes combined)			
Calendar year	0.964 (0.944, 0.984)*	0.976 (0.952, 1.001)	0.941 (0.909, 0.973)*
Diabetes (yes vs no)	8.049 (7.533, 8.602)*	8.488 (7.835, 9.198)*	7.251 (6.491, 8.102)*
Male vs female	2.571 (2.469, 2.681)*	–	–
Age (years)[a]			
≥80	31.797 (28.487, 35.592)*	27.494 (24.137, 31.43)*	39.408 (32.537, 48.219)*
70–79	23.237 (20.83, 25.996)*	22.855 (20.123, 26.057)*	23.646 (19.455, 29.022)*
60–69	15.691 (14.06, 17.561)*	16.132 (14.207, 18.388)*	13.513 (11.058, 16.665)*
50–59	10.162 (9.078, 11.404)*	9.556 (8.383, 10.932)*	11.6 (9.476, 14.326)*
40–49	3.826 (3.346, 4.378)*	3.888 (3.333, 4.543)*	3.609 (2.812, 4.642)*
Diabetes × calendar year	0.960 (0.934, 0.986)*	0.963 (0.933, 0.995)*	0.944 (0.901, 0.989)*
Minor amputation			
Model 1a (diabetes)			
Calendar year	0.954 (0.945, 0.962)*	0.957 (0.948, 0.967)*	0.946 (0.932, 0.961)*
Male vs female	2.528 (2.458, 2.599)*	–	–

Table 2 (continued)

Variables	RR (95% CI)		
	Total population	Men	Women
Age (years)[a]			
≥80	12.957 (11.216, 14.968)*	9.039 (7.666, 10.658)*	22.655 (17.640, 29.096)*
70–79	10.248 (8.874, 11.835)*	7.327 (6.221, 8.631)*	17.735 (13.805, 22.785)*
60–69	8.215 (7.112, 9.490)*	6.204 (5.267, 7.307)*	12.224 (9.498, 15.732)*
50–59	5.897 (5.095, 6.826)*	4.576 (3.878, 5.401)*	7.918 (6.117, 10.250)*
40–49	3.174 (2.709, 3.719)*	2.356 (1.968, 2.821)*	5.048 (3.829, 6.655)*
Model 1b (no diabetes)			
Calendar year	0.973 (0.959, 0.988)*	0.963 (0.944, 0.982)*	0.986 (0.965, 1.008)
Male vs female	1.541 (1.477, 1.608)*	–	–
Age (years)[a]			
≥80	40.665 (37.649, 43.924)*	42.094 (37.984, 46.65)*	37.438 (33.474, 41.872)*
70–79	19.135 (17.641, 20.756)*	20.454 (18.394, 22.744)*	17.29 (15.329, 19.503)*
60–69	8.984 (8.243, 9.792)*	10.976 (9.845, 12.238)*	6.586 (5.755, 7.537)*
50–59	4.66 (4.249, 5.110)*	5.298 (4.714, 5.954)*	3.843 (3.331, 4.434)*
40–49	1.944 (1.736, 2.177)*	2.143 (1.858, 2.471)*	1.683 (1.410, 2.010)*
Model 2 (both diabetes and no diabetes combined)			
Calendar year	0.973 (0.954, 0.992)*	0.962 (0.939, 0.987)*	0.986 (0.962, 1.010)
Diabetes (yes vs no)	9.457 (8.906, 10.045)*	11.955 (11.100, 12.882)*	6.448 (5.937, 7.003)*
Male vs female	2.088 (2.016, 2.165)*	–	–
Age (years)[a]			
≥80	25.967 (23.733, 28.462)*	23.172 (20.694, 26.017)*	28.283 (25.173, 31.882)*
70–79	16.864 (15.410, 18.488)*	15.823 (14.146, 17.747)*	17.48 (15.518, 19.753)*
60–69	11.615 (10.609, 12.739)*	12.019 (10.751, 13.473)*	9.399 (8.303, 10.669)*
50–59	6.896 (6.273, 7.592)*	7.448 (6.639, 8.376)*	5.241 (4.585, 6.003)*
40–49	2.731 (2.431, 3.068)*	2.894 (2.516, 3.33)*	2.392 (2.031, 2.816)*
Diabetes × calendar year	0.979 (0.956, 1.003)*	0.993 (0.964, 1.023)*	0.96 (0.928, 0.992)*

[a] All age groups are compared with the reference category, 0–39 years

*$p < 0.05$ vs reference category

whole observation period, the RR of a minor LEA in the population with diabetes compared with the population without diabetes was 9.457 (8.906, 10.045). This relative risk did not change significantly between 2009 and 2013 (RR interaction diabetes × calendar year: 0.979; 0.956, 1.003; Table 2). The minor LEA AR was more than twofold higher in men compared with women. The decrease in minor LEA AR in the population with diabetes was more pronounced in women, while in the population without diabetes it was more prominent in men.

Any amputation In total, 12,899 people underwent any LEA (62% men, 56% with diabetes; mean age 70 years) (ESM Table 2). We observed a substantial decline in the any amputation rate (ESM Fig. 1) in the population with diabetes, from 122.2 per 100,000 person-years in 2009 to 100.4 in 2013, 5% annual reduction; RR per calendar year 0.946; 95% CI 0.938, 0.954) (ESM Table 3). Likewise, this rate decreased moderately but significantly in the population without diabetes, from 14.1 in 2009 to 13.0 in 2013 (2% annual decrease; RR per calendar year 0.98; 95% CI 0.967, 0.994). As a result, the RR, which compared people with and without diabetes, decreased significantly (interaction diabetes × calendar year: $p < 0.001$). Regarding time trend, the results were comparable in both sexes. The any amputation rate was more than twice as high in men as in women, with greater differences in the population with diabetes.

Discussion

In this analysis over 5 years based on national health insurance data covering almost the entire population of Belgium, we found a substantial decline in the major amputation rate in people with diabetes, which was even more evident considering major amputation above the knee. In contrast, the major amputation rate remained unchanged in people without

diabetes. Thus, the RR comparing people with and without diabetes decreased but remained high. A moderate decrease in minor LEAs was observed among people with and people without diabetes.

Important differences Although a number of studies have analysed amputation risk in people with diabetes, population-based and specifically nationwide studies analysing amputation risk in populations with and without diabetes are still limited. Studies differ significantly in terms of study design, as some studies counted every hospitalisation or every LEA, rather than just the first LEA in each year, as in our study. Some studies also only estimated crude incidence rates, which were usually considerably higher in the population with diabetes compared with our study, which estimated age-adjusted incidence rates [8]. Consequently, it is difficult to make correct comparisons between them. Only a few studies are partially comparable to our study in Belgium since they also counted one LEA per person [9–11, 14, 15]. These studies found LEA incidence rates among individuals with diabetes, which are well in line with our results (e.g. about 48 per 100,000 person-years in Finland in 2007 [15], about 36 per 100,000 person years in Italy in 2010 [14]; in our study between 30 and 42 per 100,000 person years).

Our finding concerning the time trend for major LEAs in the population with diabetes, with 8% reduction per calendar year, is in line with results from international studies, which mainly demonstrated a decrease in the incidence of major LEAs among people with diabetes [10, 14, 15, 17–19]. The annual reduction in these studies ranged from 5% [14] to 7% [17] per calendar year.

In contrast, epidemiological studies showed conflicting results regarding major amputation rates in the population without diabetes. In our study and in a previous German study [10] the risk of amputation among people without diabetes was stable. However, two other European studies reported a significant reduction in this rate [14, 15].

LEAs have a huge impact on the individual, their relatives and the community [1, 2, 4]. LEAs are related to an increased mortality risk of over 50% at 5 years. Higher age, more proximal amputations and presence of peripheral arterial disease, diabetes or renal insufficiency are factors that increase this mortality risk [1]. A substantial proportion of LEAs, particularly in people with diabetes, are preventable via the provision of appropriate healthcare [20]. Much effort has been made to reduce the amputation risk in the population with diabetes, e.g. the introduction of foot centres and cooperative care between general practitioners and diabetes specialists. Recent literature has not only shown relevant regional differences in major amputation rates [21], but also the inverse correlation of these rates with the provision of specialised diabetic foot care services [22].

Our data suggest that these efforts may have achieved positive effects, as the amputation risk in the population with diabetes decreased significantly, whereas it decreased to a less-clear extent in the population without diabetes. Nevertheless, when we consider the reduction in the major LEA amputation rate in the population with diabetes, it is still sixfold higher compared with people without diabetes. Hence, further efforts are needed to prevent diabetic foot ulcers.

Strengths and weaknesses of the study Several limitations have to be considered. First, the algorithm that was used to define diabetes status is based on reimbursed treatment, not on diagnosis. A careful assumption was made, based on inclusion in a diabetes care system and/or medical treatment with diabetes-specific medication and/or registration of repeated measurements of HbA_{1c}. Inclusion in a diabetes care system is a clear indicator for a diagnosis of diabetes. Diabetes-related medical treatment is somewhat less precise in the case of metformin, as this can also be used for the treatment of obesity and polycystic ovary syndrome, although this is probably negligible in an older population. Repeated HbA_{1c} measurements suggest the presence of diabetes.

Second, as we used data from national health insurances, clinical data are unavailable, as are other variables such as socioeconomic status.

A key strength of our study is that we were able to analyse a nationwide dataset covering almost the entire Belgian population stratified by diabetes status and amputation level. Therefore, our study is—to our best knowledge—one of the few to report LEAs in a national population. Furthermore, our data on the number and type of LEAs are reliable as they are based on the same reimbursement data collected by the IMA/AIM. In addition, this study is based on a continuous 5 year observation period, and not on periodic sampling, in order to avoid methodological bias over time.

Unanswered questions and future research The major amputation rate in Belgium gradually declined during the study period in people with diabetes, which was particularly evident for major amputation above the knee. A weaker but also significant decrease was observed in minor amputation rate in people with, as well as those without, diabetes. In contrast, no change in any major LEA was found in individuals without diabetes. Despite all efforts to date, a large number of people still undergo major amputations. Considering the observed results, namely reductions in both major and minor amputation rates, to be a potential result of the implementation of specialised diabetic foot care services, nationwide coverage of such institutions and unrestricted access for individuals in need should be discussed as a primary future goal.

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Data availability The data that support the findings of this study are available from IMA/AIM, but restrictions apply to the availability of these data, which were used under licence for the current study and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of IMA/AIM.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement HC performed data analysis and interpretation and drafted the manuscript. PL designed the study and drafted the manuscript. MN researched data and contributed to the concept, design and drafting of the manuscript. WA, JG and HA prepared and extracted data and contributed to the data interpretation and discussion. TK and SM contributed to the data interpretation and discussion. JB, CVH, FN, KD, ID and PF contributed to the concept and design and to the data interpretation. KVA and AI designed the study and contributed to the concept, design, data interpretation and discussion. All authors critically reviewed and approved the final manuscript. AI and KVA are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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