Masterarbeit

„Darstellung der geschätzten Prävalenz einer chronischen Nierenerkrankung steirischer Patient*innen mittleren Alters“

eingereicht von

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Graz, am 8. August 2024

Eidesstattliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die vorliegende Arbeit selbstständig und ohne fremde Hilfe verfasst habe, andere als die angegebenen Quellen nicht verwendet habe und die den benutzten Quellen wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe.

Graz, am 8. August 2024 Unterschrift eh

Danksagungen

Zuallererst gilt mein besonderer Dank Herrn Research Prof. PD Dr. Alexander Avian und Frau Univ.-Prof. Dipl.-Ing. Dr. Andrea Berghold, die zu meiner großen Freude zugestimmt haben, mich zu betreuen. Wir arbeiten bereits seit vielen Jahren im Rahmen zahlreicher gemeinsamer Forschungsprojekte erfolgreich zusammen, so auch im Rahmen des Projekts „niere.schützen 2.0“, weshalb auch vor Beginn der Betreuungsarbeit die explizite Zustimmung für die Betreuung von Seiten des Vizerektorats für Studium und Lehre 2023 erfolgte. Ziel dieser Masterarbeit war das Verfassen eines Manuskripts zur Baseline-Erhebung und wiederum waren es Herr PD Avian und Frau Univ.-Prof. Dipl.-Ing. Dr. Berghold, welche mir in einem lebhaften und interaktiven Dialog wertvolles Feedback zur Arbeit für einen erfolgreichen Abschluss gegeben haben.

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Zusammenfassung

Hintergrund und Ziele: Die globale Gesundheitsbelastung durch chronische Nierenerkrankungen (CKD) ergibt sich sowohl aus der Krankheit selbst als auch aus den zahlreichen damit verbundenen Gesundheitsproblemen. Ziel dieser Studie war es, die Prävalenz von bisher unerkannter CKD bei Patient*innen mittleren Alters mit Risikofaktoren für CKD zu schätzen. Identifizierte Patient*innen wurden in das steirische Awarenessprogrogramm „niere.schützen 2.0“ aufgenommen und Daten zu ihrer Demographie, zu Risikofaktoren und zur Nierenfunktion beschrieben.

Methode: Es erfolgte eine Analyse der Ausgangsdaten aus der „niere.schützen 2.0“-Studie von 40-65-jährigen Patient*innen mit mindestens einem Risikofaktor für CKD (arterielle Hypertonie, Diabetes mellitus, kardiovaskuläre Erkrankungen, Adipositas oder familiär bedingte terminale Niereninsuffizienz). Die Teilnehmer*innen galten als Patient*innen mit bisher unerkannter CKD, wenn ihre geschätzte glomuläre Filtrationsrate (eGFR) weniger als 60 ml/min/1,73 m2 und/oder ein Albumin-Kreatinin-Verhältnis (ACR) ≥ 30 mg/g betrug. Der Anteil der Patient*innen mit bisher unerkannter CKD wurde erhoben, und Einflussgrößen wurden in einer multivariablen Analyse untersucht.

Ergebnisse: Insgesamt wurden 749 Teilnehmer*innen in diese Analyse einbezogen. Die Prävalenz einer zuvor unerkannten CKD in einer Risikopopulation wurde auf 20,1 % (95% CI: 17,1 - 23,6) geschätzt. Die multivariable Analyse zeigte, dass Alter (OR 1,06, 95% CI: 1,02 - 1,09), Diabetes mellitus (OR 1,65, 95% CI: 1,12 - 30 2,30) und Adipositas (OR: 1,55, 95% CI: 1,04 - 2,30) unabhängige Prädiktoren für CKD sind. Die Mehrheit der Patient*innen mit zuvor unerkannter CKD hatte eine Albuminurie der Kategorie A2-A3 (121 von 150). Die meisten Patient*innen mit einer zuvor unerkannten eGFR < 60 ml/min/1,73 m2 befanden sich im Stadium G3 (36 von 39 Patient*innen).

Zusammenfassung: Durch ein pragmatisches, gezieltes, risikobasiertes Screening auf CKD in der Primärversorgung konnte eine beträchtliche Anzahl von Patient*innen mittleren Alters mit zuvor unerkannter CKD identifiziert werden. Dadurch wird sichergestellt, dass diese Patient*innen nicht übersehen werden und zukünftig eine optimierte Versorgung erhalten. Somit könnte diese Maßnahme möglicherweise das Fortschreiten der Niereninsuffizienz verlangsamen und damit verbundene kardiovaskuläre Ereignisse verhindern.

Abstract in English

Introduction and aim: The global health burden of chronic kidney disease (CKD) results from both the disease itself and the numerous health problems associated with it. The aim of this study was to estimate the prevalence of previously undetected CKD in middle-aged patients with risk factors for CKD. Identified patients were included in the Styrian nephrology awareness program "kidney.care 2.0" and data on their demographics, risk factors and kidney function were described.

Methods: A cross-sectional analysis of baseline data derived from the "kidney.care 2.0" study of 40-65 year old patients with at least one risk factor for CKD (hypertension, diabetes, cardiovascular disease, obesity or family history of end-stage kidney disease) was performed. Participants were considered to have previously undetected CKD if their estimated glomular filtration rate (eGFR) was less than 60 ml/min/1.73 m2 and/or albumin creatinine ratio (ACR) ≥ 30 mg/g. The prevalence of previously unrecognised CKD was calculated and multivariate analyses were carried out.

Results: A total of 749 participants were included in this analysis. The prevalence of previously undetected CKD in an at-risk population was estimated at 20.1% (95%CI: 17.1 – 23.6). Multivariable analysis showed age (OR 1.06, 95%CI: 1.02 – 1.09), diabetes mellitus (OR 1.65, 95%CI: 1.12 – 30 2.30) and obesity (OR: 1.55, 95%CI: 1.04 – 2.30) to be independent predictors of CKD. The majority of patients with previously undetected CKD had category A2-A3 albuminuria (121 out of 150). Most patients with previously undetected eGFR < 60 ml/min/1.73 m2 were in stage G3 (36 out of 39 patients).

Conclusion: Pragmatic, targeted, risk-based screening for CKD in primary care successfully identified a significant number of middle-aged patients with previously undetected CKD and addressed the problem of these patients being overlooked for future optimized care. The intervention may slow progression to kidney failure and prevent related cardiovascular events.

Abkürzungsverzeichnis

ACR	Albumin-Kreatinin-Ratio
CKD	Chronic Kidney Disease (chronische Nierenerkrankung)
eGFR	estimated glomerular filtration rate, geschätzte glomeruläre Filtrationsrate
GFR	glomerular filtration rate, glomeruläre Filtrationsrate
IAMEV	Institut für Allgemeinmedizin und evidenzbasierte Versorgungsforschung, Medizinische Universität Graz
IMI	Institut für Medizinische Informatik, Statistik und Dokumentation, Medizinische Universität Graz
KDIGO	Kidney Disease Improving Global Outcomes
ÖGK	Österreichische Gesundheitskasse
PVEs	Primärversorgungseinheiten

Inhaltsverzeichnis

1 Einleitung

Die Chronische Nierenerkrankung (engl. chronic kidney disease, CKD) ist definiert durch eine Nierenfunktionseinschränkung mit einer eGFR < 60 ml/min/1,73 m2 und/oder eine Nierenschädigung mit einer Albuminurie ≥ 30 mg/g über mindestens drei Monate [1]. Diabetes mellitus, arterielle Hypertonie [2-4], Adipositas [2-7] und Herz-Kreislauf-Erkrankungen [7-9] stellen die häufigsten Ursachen für CKD dar. Weiters sind Patient*innen mit der Einnahme von potenziell nierenschädigenden Medikamenten sowie Personen mit erblich bedingten Nierenerkrankungen oder Personen mit einer positiven CKD-Familienanamnese einem höheren Risiko für das Auftreten einer CKD ausgesetzt [10]. Weltweit wird die CKD-Prävalenz in der Allgemeinbevölkerung auf drei bis 18 Prozent in Abhängigkeit vom Land geschätzt [11-14]. Ein Anstieg der CKD-Prävalenz mit zunehmenden Alter ist zum Teil physiologisch bedingt, da die Nierenfunktion im Alter abnimmt [15]. Kleine Schwankungen der eGFR und der Albuminurie sind häufig und nur nach rezidivierenden Kontrollen ist eine klare Diagnostik bzw. Verlaufskontrolle bezüglich einer Progression möglich [1].

Für ein routinemäßiges CKD-Screening bei asymptomatischen Patient*innen ohne vorliegende Risikofaktoren liegt eine unzureichende Evidenz hinsichtlich eines Nutzens bzw. Schadens vor [16-19] und sollte nicht in der Gesamtbevölkerung durchgeführt, sondern nur bei jenen Bevölkerungsgruppen, die ein hohes Risiko aufweisen, an CKD zu erkranken.

1.1 Steirisches Awarenessprogramm „niere.schützen”

2013 wurde ein Konzept von der Österreichischen Gesellschaft für Nephrologie vorgelegt, welches ein CKD-Screening im niedergelassenen Bereich forderte und in Folge wurde die Entwicklung eines Umsetzungskonzeptes vom Land Steiermark und der Österreichischen Gesundheitskasse beschlossen [20]. Seit 2015 ist auch das Institut für Allgemeinmedizin und evidenzbasierte Versorgungsforschung (IAMEV) an der Medizinischen Universität Graz involviert [21] und 2016 startete das Awarenessprogramm „niere.schützen” in der Steiermark mit dem Ziel bei 40- bis 65-jährigen Risikopatient*innen (Hypertoniker*innen, Diabetiker*innen, Personen mit Adipositas, Herz-Kreislauf-Erkrankte, Personen mit terminaler Niereninsuffizienz in der Familie) im hausärztlichen Setting eine potenzielle existente CKD frühzeitig zu erkennen. Durch die Bestimmung der eGFR und ACR könnte die Nierenfunktion und eine mögliche Schädigung frühzeitig erkannt und fachgerecht behandelt werden. Hierfür wurden von den Nephrolog*innen in Zusammenarbeit mit dem IAMEV ein Kontrollschema von der KIDGO adaptiert und mit den Hausärzt*innen pilotiert und hinsichtlich der Anwendung [21] untersucht. Das initiale „niere.schützen“-Programm wurde von den Hausärzt*innen nicht angenommen, sodass mittels leitfadengestützter Interviews Hausärzt*innen bzgl. ihrer motivierenden als auch hemmenden Faktoren für die Programmumsetzung befragt wurden. Obwohl das Awarenessprogramm als versorgungsrelevant eingestuft wurde, wurden als mögliche Barrieren hoher Zeitaufwand, die Komplexität des Programms und ein Mangel an verfügbaren Nephrolog*innen sowie die fehlende monetäre Abgeltung genannt [22].

Dies führte dazu, dass, finanziert über den Gesundheitsfonds Steiermark und die Österreichische Gesundheitskasse (ÖGK), 2021 „niere.schützen 2.0” gestartet wurde. Die Steiermärkische Krankenanstaltengesellschaft (KAGES) ist die Fördernehmerin von „niere.schützen 2.0“ und beauftragte die Klinische Abteilung für Nephrologie des Universitätsklinikums Graz sowie das Institut für Allgemeinmedizin und evidenzbasierte Versorgungsforschung (IAMEV) und das Institut für Medizinische Informatik, Statistik und Dokumentation (IMI) an der Medizinischen Universität Graz mit der Umsetzung des Projektes mit dem Ziel, nicht nur das Bewusstsein der Hausärzt*innen zu schärfen, sondern auch die Kommunikation zwischen Hausärzt*innen und Nephrolog*innen zu verbessern, die Patient*innenaufklärung zu verbessern und die Prävalenz von CKD in einer Risikopopulation zu schätzen [23].

Das primäre Ziel der in dem von der Autorin publizierten Manuskripts als Basis für die publikationsbasierte Masterarbeit war die Beschreibung der Studie zur Schätzung der Prävalenz von bisher unentdeckter CKD bei Patient*innen mittleren Alters mit Risikofaktoren für CKD. Das sekundäre Ziel war es, die Teilnehmer*innen des steirischen Nephrologie-Aufklärungsprogramms „kidney.care 2.0“ hinsichtlich ihrer Demographie, Risikofaktoren und Nierenfunktion zu klassifizieren.

2 Zur Publikation

2.1 Publikation

Andrea Siebenhofer, Christine Loder, Alexander Avian, Elisabeth Platzer, Carolin Zipp, Astrid Mauric, Ulrike Spary-Kainz, Andrea Berghold, Alexander R. Rosenkranz; **Prevalence of undetected chronic kidney disease in high-risk middle-aged patients in primary care: a cross-sectional study**.

Dieses Manuskript wurde am 11. April 2024 bei Frontiers in Medicine eingereicht. Am 29.7. 2024 wurde das Manuskript zur Veröffentlichung akzeptiert.

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Impact Factor: 3.1
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Im Anhang 1 befindet sich die finale Version des Manuskripts.

2.2 Reviewerkommentare

Dieses Manuskript wurde von einem Section Editor (Udeme Ekrikpo) und zwei externen Reviewer*innen (Maria-Eleni Roumelioti, Jean-Francois Chenot) begutachtet, wobei anzumerken ist, dass keinerlei Zusammenarbeit mit diesen Personen besteht und diese daher völlig unabhängig das Review erstellt haben.

Am 23. Juni erfolgte die erste und am 23. Juli 2024 die zweite Wiedereinreichung mit einer detaillierten Beantwortung der Kommentare.

Im Anhang 2 und Anhang 3 befinden sich die detaillierten Stellungnahmen zu den jeweiligen Anmerkungen.

3 Darstellung des eigenen Anteils

Die Arbeit wurde als Förderprojekt des Gesundheitsfonds Steiermark mit der Fördernehmerin der Steiermärkische Krankenanstaltengesellschaft am Institut für Allgemeinmedizin und evidenzbasierte Versorgungsforschung, an der Universitätsklinik für

Innere Medizin, Klinische Abteilung für Nephrologie sowie am Institut für Medizinische Informatik, Statistik und Dokumentation der Medizinischen Universität Graz durchgeführt.

Die Autorin der vorliegenden Arbeit, Andrea Siebenhofer-Kroitzsch, beschäftigt sich bereits seit 2015 mit der Implementierung des Awarenessprogramms „niere.schützen" in steirischen Hausarztpraxen [20-23]. Aufgrund der unzureichenden Teilnahmezahl am ursprünglichen Programm wurde von der Autorin federführend das Nachfolgeprojekt: „niere.schützen 2.0" initiiert und neben den strategischen Maßnahmen zur Steigerung der Teilnehmer*innenzahl auch ein Forschungsprojekt entwickelt. Eine Studie dieser Größenordnung ist nur durch die Mitarbeit vieler Personen möglich, wobei das gewählte Studiendesign und die Fragestellung maßgeblich von der Autorin vorgegeben und im Team abgestimmt wurden. Die Datenerhebung und -auswertung für die Baseline-Erhebung hatte zum Zeitpunkt des Beginns der Masterarbeit bereits stattgefunden, da diese Studie in der vorliegenden Form in der für die Erstellung der Masterarbeit zur Verfügung stehenden Zeit nicht durchführbar gewesen wäre.

Ziel dieser Masterarbeit war daher die Erstellung des Publikationsmanuskripts basierend auf einer mehrjährigen Studienphase (2020 – ongoing bis Ende 2024). Im Nachfolgenden werden die Beiträge jedes*r Co-Autors*in offengelegt, um basierend auf dem Vancouver Statement der „Uniform Requirements for Manuscripts Submitted to Biomedical Journals" zu belegen, dass substantielle Beiträge für eine begründete Co-Autorenschaft geleistet wurden:

> C. Loder und A. Rosenkranz sind Bestandteil des Kernteams und waren ins gesamte Arbeitsprogramm eingebunden. Die Co-Autorenschaft von E. Platzer, C. Zipp begründet sich dadurch, dass sie bei der inhaltlichen Ausgestaltung des Studienprotokolls, der Datenerhebung, beim Projekt- und Datamanagement beteiligt waren. A. Mauric war als klinische Nephrologin primäre Ansprechpartnerin in fachlichen Belangen, war Vortragende bei Qualitätszirkelfortbildungen und führte die Plausibilitätsprüfungen bei den erhoben Outcomes durch. U. Spary-Kainz war als Ärztin für Allgemeinmedizin primäre Ansprechpartnerin in fachlichen Belangen für den hausärztlichen Bereich tätig, war Vortragende bei Qualitätszirkelfortbildungen und für die Erstellung der Materialien für den niedergelassenen Bereich zuständig. Die Datenauswertung erfolgte zum

überwiegenden Teil von A. Avian und A. Berghold, wobei sie in sämtliche Arbeitsprozesse eingebunden waren.

Die Masterarbeit umfasste die Erstellung des Publikationsmanuskripts, wobei die Details für die Leistungen sämtlicher Personen in der Tabelle im Anhang 4 dargelegt werden.

4 Diskussion der Gesamtheit der Ergebnisse und deren Beitrag für die Beantwortung der Fragestellung

Es konnten insgesamt 25 Hausärzt*innenpraxen und acht PVEs in der Steiermark für die Projektteilnahme bei „niere.schützen 2.0“ rekrutiert werden, wovon 749 Patient*innen ins Projekt eingeschlossen werden konnten. Die Ergebnisse der Prävalenzschätzung zeigten bei insgesamt 20,1 % (95% CI 17,1 – 23,6) der eingeschlossenen Patient*innen eine bisher unerkannte CKD. Die Auswertung nach Risikogruppen zeigte, dass die CKD-Prävalenz mit dem Alter steigt, mehr Diabetiker*innen im Vergleich zu Patient*innen ohne Diabetes mellitus sowie adipöse Patient*innen ein höheres Risiko aufweisen.

Eine detaillierte Diskussion der Ergebnisse findet sich in der Diskussion der Publikation im Anhang 1.

4.1 Besonderheit des Gesamtprojekts „niere.schützen 2.0“ für zukünftige Versorgungsforschungsprojekte im niedergelassenen Bereich

Erstmalig gab es in Österreich eine groß angelegte Initiative, um Versorgungsforschung im niedergelassenen hausärztlichen Bereich durchzuführen. Hierfür war es erforderlich, zahlreiche Initiativen zu setzen, um durch verschiedene Fortbildungsveranstaltungen und zielgruppengerichtete Öffentlichkeitsarbeit das hausärztliche Interesse für eine Teilnahme zu gewinnen. Schlussendlich ist es uns gelungen, 33 Hausärzt*innen und 749 Patient*innen ins Projekt einzuschließen. „niere.schützen 2.0“ war damit das größte Projekt zur Schätzung der Prävalenz bisher unerkannter CKD bei Risikogruppen in Österreich und zugleich meines Wissens das erste Projekt für eine erfolgreiche Durchführung einer pragmatischen klinischen Studie im hausärztlichen Setting.

Da es auch zum Teil bedingt durch die Covid-19-Pandemie zahlreiche Rekrutierungsprobleme gab, wurden im Rahmen der Anwendungsbeobachtung zahlreiche Gründe aufgedeckt, die uns wiederum für weitere geplante Studien im niedergelassenen Bereich wichtige Hilfestellungen geben werden. Als wesentliche primäre Gründe für die Verzögerung wurden fehlende zeitliche Ressourcen, eine hohe Arbeitslast z.B. für Impfungen im Rahmen der Covid-19-Pandemie genannt. Aber auch Probleme beim Screening für den Einschluss der Patient*innen wurden vorgebracht. Als eine wesentliche Maßnahme wurde von Seiten des Studienteams eine aktive Unterstützung vor Ort durch Projektmitarbeiter*innen des IAMEV angeboten, weshalb dieses Projekt erfolgreich zum Abschluss gebracht wurde.

Nach der Veröffentlichung der Daten der Baseline-Erhebung wird ein weiteres Manuskript erstellt, nachdem die Daten des Follow-up nach 12 Monaten final ausgewertet wurden.

Das absolut wichtigste Ergebnis dieses Projektes – unabhängig von den praktisch relevanten Fakten, die zu einer Optimierung der hausärztlichen nephrologischen Versorgung dienen sollen – war der Aufbau von Wissen im Team des Instituts für Allgemeinmedizin und evidenzbasierte Versorgungsforschung, um zukünftig weitere pragmatische versorgungsrelevante Studien im niedergelassenen primärärztlichen Bereich erfolgreich abwickeln zu können.

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6 Anhang

Anhang 1: Finale Version des Manuskripts

Prevalence of undetected chronic kidney disease in high-risk middle-aged patients in primary care: a cross-sectional study

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Abstract

Introduction: The global health burden of chronic kidney disease (CKD) results from both the disease itself and the numerous health problems associated with it. The aim of this study was to estimate the prevalence of previously undetected CKD in middle-aged patients with risk factors for CKD. Identified patients were included in the Styrian nephrology awareness program "kidney.care 2.0" and data on their demographics, risk factors and kidney function were described.
Methods: Cross-sectional analysis of baseline data derived from the "kidney.care 2.0" study of 40-65 year old patients with at least one risk factor for CKD (hypertension, diabetes, cardiovascular disease, obesity or family history of end-stage kidney disease). Participants were considered to have previously undetected CKD if their estimated glomular filtration rate (eGFR) was less than 60 ml/min/1.73 m^2 and/or albumin creatinine ratio (ACR) $\geq$ 30 mg/g. We calculated the prevalence of previously undetected CKD and performed multivariate analyses.
Results: A total of 749 participants were included in this analysis. The prevalence of previously undetected CKD in an at-risk population was estimated at 20.1% (95%CI: 17.1

– 23.6). Multivariable analysis showed age (OR 1.06, 95%CI: 1.02 – 1.09), diabetes mellitus (OR 1.65, 95%CI: 1.12 – 2.30) and obesity (OR: 1.55, 95%CI: 1.04 – 2.30) to be independent predictors of CKD. The majority of patients with previously undetected CKD had category A2-A3 albuminuria (121 out of 150). Most patients with previously undetected eGFR < 60 ml/min/1.73 m^2 were in stage G3 (36 out of 39 patients).
Conclusion: Pragmatic, targeted, risk-based screening for CKD in primary care successfully identified a significant number of middle-aged patients with previously undetected CKD and addressed the problem of these patients being overlooked for future optimized care. The intervention may slow progression to kidney failure and prevent related cardiovascular events.

1 Introduction

The global health burden of chronic kidney disease (CKD) results from both the disease itself and the numerous health problems including cardiovascular issues that are associated with it (1-3). Almost one billion people worldwide (4) suffer from kidney disease, with prevalence across the world varying from around 3% to 18%, depending on country (5, 6). Many risk factors such as diabetes, hypertension, and obesity (7, 8) are associated with increased prevalence of CKD (9, 10) as is multimorbidity (9, 11).
Not only is early-stage CKD often asymptomatic (12), but despite laboratory evidence it frequently remains undiagnosed (13-15). In a large study of the digital health records of millions of patients, two-thirds of patients whose laboratory data indicated the presence of CKD had not been diagnosed as having the disease (13). Based on digital records from five countries, Tangri et al. demonstrated that most cases of stage G3 CKD (estimated glomular filtration rate (eGFR) ≥ 30 and < 60 ml/min/1.73 m^2) are not diagnosed and lack an International Classification of Diseases (ICD) 9/10 diagnosis code, despite the documentation of reduced GFR in patients' records (14). Clinical data from a huge population-based cohort conducted as part of the Study of Health in Pomerania (SHIP-START) showed that only 5% of patients had an ICD code for a diagnosis of CKD although 20% had an eGFR <60ml/min/1.73m2 60 or albuminuria ≥30 mg/gl (15). In a systematic review from 2020, Neale et al. explain that a lack of ICD coding does not necessarily mean CDK is not noticed and provide a number of reasons for it. These include CKD not being the main medical problem, combined with a lack of time, limited access to specialist nephrologists, software systems that do not automatically flag abnormal results, fear of frightening patients by diagnosing such an illness, and concerns about stigmatization. Last but not least, diagnostic challenges may further result from unclear definitions of CKD and consequent dissatisfaction with CKD guidelines (16). An analysis by Friedl et al 2013, which compared routine laboratory parameters with the actual documentation of ICD-10 diagnoses of CKD in patients' discharge reports, also showed that CKD often goes undetected, even in a hospital setting (17). Another study that evaluated over 9,000 patients in a primary care setting showed that > 50 % of CKD stage G3-5 patients were not diagnosed with CKD and received a lower level of care than patients that had been diagnosed with CKD (18). Most people with mild CKD presented in primary care practices, and in several countries initiatives aimed at improving the identification and management of CKD already exist (19-22).
Beneficial screening programs should do more good than harm (23). For CKD, many bodies such as NICE (24), the American College of Physicians (ACP) (25), the US Preventive Service Task Force (USPSTF) (26) and the Agency of Healthcare Research and Quality (27) have recommended against population-wide screening due to concerns about overdiagnosis, unnecessary treatment of normal age-related decline in kidney function, a high number of tests associated with further event-related diagnostic investigations, and

excessive cost. In 2021, the conclusions of the Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference were published, which recommended CKD screening coupled with risk stratification in a primary or community care setting, followed by immediate treatment for high-risk individuals (28). The procedure of filtering out high-risk patients prior to conducting laboratory tests has been evaluated in several studies over the past 20 years (19, 21, 29). It has also recently been carried out in the Pan-Canadian See Kidney Disease (SeeKD) Targeted Screening Program, in which patients with at least one risk factor underwent laboratory tests and were provided with subsequent information and tailored treatment (20).
In Austria, the nephrology awareness program “niere.schützen” (“kidney.care”) was launched in a primary care setting in the state of Styria for people at risk of kidney failure (30). General practitioners (GPs) were routinely provided with evidence-based information materials on diagnosis, treatment and referral procedures, but only a minority of GPs participated in the awareness program. The opinions of Styrian GPs were evaluated and several factors aimed at increasing its attractiveness were identified. These included further education for doctors, the need for more contacts among nephrologists, and financial incentives for carrying out laboratory tests (31). At the same time, we searched for existing international nephrological screening and support programs in order to identify further evaluation parameters and screening concepts (32). Finally, in January 2021, we launched “niere.schützen 2.0” (“kidney.care 2.0”), with the aim of not only raising awareness among GPs, but enhancing communication between GPs and nephrologists, improving patient education, and estimating the prevalence of CKD in a risk population (33). In line with recommendations on program evaluation, we conducted patient-centered labelling (34).
The primary objective of the study described in this manuscript was to estimate the prevalence of previously undetected CKD in middle-aged patients with risk factors for CKD (Table 1). Our secondary aim was to classify participants in the Styrian nephrology awareness program “kidney.care 2.0” in terms of their demographics, risk factors and kidney function.

Table 1 Risk factors for CKD according to the “kidney.care” program

Arterial hypertension (documented diagnosis of hypertension for at least 3 months, defined as systolic blood pressure > 140 or diastolic blood pressure > 90 mmHg)
Diabetes mellitus (defined as type 1 and type 2)
Obesity (defined as body mass index > 30 kg/m^2)
History of cardiovascular diseases (stroke, transient ischemic attack (TIA), coronary heart disease, peripheral arterial disease)
End-stage kidney disease in the family (family defined as children, parents and siblings)

2 Methods

2.1 Study design and outcomes

We conducted a cross-sectional analysis of baseline data from the “kidney.care 2.0” study. Over a 24-month period lasting from January 2021 to December 2022, GPs in Styria (Austria) screened patients aged 40-65 years for the presence of at least one CKD risk factor (Table 1). Each GP was expected to screen all at-risk patients attending his or her practice over an 8-week period, which could be extended if necessary in consultation with the study team, as was frequently the case due to the COVID pandemic in 2020-2022 (34).

Inclusion criteria were men and women of all ethnic groups, aged between 40 and 65 years, treated by a GP with a health insurance contract, the provision of written consent to participate in the study, and with at least one of the risk factors for CKD (Table 1). Patients were excluded if GPs' records showed they had a prior diagnosis of CKD, they had previously participated in the "kidney.care" program, had an eGFR lower than 15 ml/min/1.73 m², had received a kidney transplant, dialysis or cancer treatment, or had New York Heart Association (NYHA) heart failure > stage II. Patients with a life expectancy of less than six months or who were unable to provide informed consent according to their GP were also excluded.
For this study, participants were diagnosed with CKD if the laboratory results indicated a decrease in kidney function (eGFR < 60 ml/min/1.73 m^2) and/or evidence of kidney damage (albumin creatinine ratio (ACR) ≥ 30 mg/g). In the case of initial kidney damage (ACR ≥ 30 mg/g), a second ACR was assessed within three months and CKD was diagnosed only if an albuminuria test was positive.
The primary outcome, based on a descriptive analysis of the baseline data of the "kidney.care 2.0" study, was the prevalence of previously undetected CKD in middle-aged at-risk patients in primary care practices. The participants' demographic characteristics, risk factors, laboratory results and concomitant medication served as secondary outcomes. The study protocol was approved by the Ethics Committee of the Medical University of Graz (reference 32-554 ex 19/20) and registered with the German Clinical Trials Register (registration number DRKS00022966). The patients/participants provided their written informed consent to participate in this study.

2.2 Recruitment and screening

To achieve the required number of 30 to 40 collaborating GPs, a variety of recruitment strategies were developed and implemented between January 2021 and December 2022. Participating GPs were asked to consecutively screen patients aged 40-65 with the defined risk factors that presented to the practice during an eight-week period (to avoid selection bias) and satisfied all other eligibility criteria. Recruitment at each individual practice ceased when 24-40 eligible patients had agreed and provided written informed consent to participate in the "kidney.care 2.0 study". If necessary, it was possible to extend the eight-week period in consultation with the study team, provided that it ended no later than December 31, 2022. For further details see Supplementary Table S1.

2.3 Data collection and patient management

Eligible patients that had provided their written informed consent attended an initial baseline visit at which the study was explained to them. At the baseline visit, blood and urine samples were collected, sent for laboratory testing and analyzed in seven laboratories that used isotope dilution mass spectrometry (IDMS) to measure serum creatinine (35). The eGFR was then reported using the CKD Epidemiology Collaboration (CKD-EPI) equation (36), and ACR was assessed. In accordance with guidelines, the eGFR values were rounded to the nearest whole number for categorization (37).
Based on the Kidney Failure Risk Equation (38), we developed an adapted and slightly simplified kidney-care referral schema (Figure 1) which was piloted with GPs and nephrologists from the Division of Nephrology, Medical University of Graz for practicability and comprehensibility (30). Prior to participation in our "kidney.care 2.0" program all GPs participated in a short training course and were provided with guidance materials for treatment and further management in accordance with the Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (KDIGO) (37). In addition, we set up a "progression outpatient clinic" at the Division of Nephrology,

Medical University of Graz, to ensure that patients could be referred there if necessary. Participating GPs also had the opportunity to discuss treatment options with a nephrologist via a dedicated “telephone hotline”.
After 12 months, all patients, irrespective of whether they had been diagnosed with CKD or not, were invited by their GP to a follow-up consultation at their primary care practice to evaluate changes in kidney function and the need for further management.

2.4 Sample size

Sample size considerations were made with respect to the precision of the prevalence estimate. According to the literature (39) and data from Austria (40), the prevalence of CKD in the at-risk population is between 14% and 24%. Since patients were recruited from different GPs practices, the precision of the prevalence estimate was influenced by the design effect DE, whereby DE = 1 + (m - 1)*ICC and m is the average cluster size and ICC the intraclass correlation coefficient. Assuming a comparable prevalence in Styria, with a sample size of n = 1,000, an ICC of 0.01 and an average cluster size of m=30 to m=100 a prevalence of 15% to 35% could be estimated with a 95% confidence interval of ±2.5 to ±4.2.

2.5 Statistical methods

Continuous baseline variables were reported as median and interquartile range or mean and standard deviation and categorical variables were reported as absolute and relative numbers. The prevalence of previously undetected CKD in the population at-risk and the 95% confidence interval were estimated using a mixed-effects logistic regression model (random effect: GP practice) based on the available sample. To evaluate the effect of the primary care practices, a sensitivity analysis was performed, excluding the random effect primary care practices, by calculating the relative proportion of affected individuals and the corresponding 95% confidence intervals.
In addition to the primary outcome, the influence of baseline characteristics on the presence of CKD was analyzed using logistic regression (outcome: CKD yes/no). Primary care practice was included in the models as a random effect. Variables with a $p < .2$ in univariable analyses were included in multivariable analyses. Before entering in the final model these variables were tested for multicollinearity. The resulting potential predictors for CKD were entered in the final analysis. Backward selection was used to determine the final model with independent significant predictors. All data management and analyses were performed using SAS (version 9.4) and R (version 4.2.1).

3 Results

Between January 2021 and December 2022, 1,092 patients in 33 primary care practices were screened for eligibility (5 to 97 per practice; median: 28). Of these, 339 could not be included (did not fulfil inclusion criteria: n = 275, no informed consent: n = 53, other reasons: n = 11) and no data were collected for a further four patients. Overall, 749 patients (3 to 65 patients per practice, median: 23) were included in the analysis (Figure 2).
Mean age of analyzed patients was 56.2 ± 6.4 years, 46.1% (n = 345) were female, and the most common risk factors were arterial hypertension (77.3%) and obesity (52.5%). Antihypertensives were the most frequently taken medications (73.9%) (Table 2).

Table 2 Baseline characteristics

		n (%)
Age		56.2 ± 6.4
Sex	male	404 (53.9%)
	female	345 (46.1%)
Arterial hypertension	No	167 (22.7%)
	Yes	569 (77.3%)
Obesity	No	343 (47.5%)
	Yes	379 (52.5%)
Diabetes mellitus (Type 1 or Type 2)	No	409 (55.3%)
	Yes	331 (44.7%)
History of cardiovascular disease	No	629 (85.1%)
	Yes	110 (14.9%)
End-stage kidney disease in the family	No	690 (95.4%)
	Yes	33 (4.6%)
Antihypertensive drugs	No	195 (26.1%)
	Yes	551 (73.9%)
Other long-term medications[a]	No	257 (34.8%)
	Yes	482 (65.2%)
Statins	No	441 (59.2%)
	Yes	304 (40.8%)
Antidiabetic drugs	No	460 (62.1%)
	Yes	281 (37.9%)
Non-steroidal anti-rheumatic drugs (NSAR)	No	648 (88.4%)
	Yes	85 (11.6%)

[a]"Other long-term medications": Platelet aggregation inhibitors (TAH), anticoagulants, proton pump inhibitors (PPI), psychotropic drugs, uricostatic drugs (allopurinol), GABA analogue, morphine/opiate, vitamins/trace elements (calcium, iron, vitamin D, folic acid), thyroid medication, bronchodilators, analgesics

Overall, 150 at-risk patients fulfilled the criteria for CKD. Mean age of these patients was 57.6 ± 5.9 years, 41.3% (n = 62) were female, and the most common risk factors were arterial hypertension (82.9%) and obesity (59.7%). Antihypertensives were the most frequently taken medications (82.7%) (Supplementary Table S2). An ACR ≥ 30 mg/g (A2-A3) was detected in 121 patients and an eGFR < 60 ml/min/1.73 m² (≤ G3) in 39. EGFR was < 30 ml/min/1.73 m² in three patients and between 30 and 59 ml/min/1.73 m² (stage G3) in 36. Ten patients were diagnosed with both albuminuria (A2-A3) and reduced kidney function (≤ G3). The prevalence of previously undetected CKD in an at-risk population was estimated to be 20.1% (95%CI: 17.1 – 23.6). The estimated prevalence was highest in patients with diabetes mellitus (25.6%, 95%CI: 20.0 – 32.0), followed by patients with obesity (22.4%, 95%CI: 17.0 – 28.9), hypertension (21.3%, 95%CI: 18.1 – 24.8) and cardiovascular diseases (20.0%, 95%CI: 13.6 – 28.5).
Univariable predictors of CKD in an at-risk population were higher age (Odds Ratio (OR): 1.05, 95%CI: 1.02 – 1.08, p = .003), diabetes mellitus (OR 1.83, 95%CI: 1.27 – 2.64, p = 0.001), antihypertensives (OR: 1.89, 95%CI 1.19 – 2.99, p = 0.007), statins (OR: 1.49, 95%CI 1.04 – 2.14, p = 0.029), antidiabetics (OR: 1.87 95%CI 1.30 – 2.68, p =0.001) and other long-term medications (OR: 1.65, 95%CI: 1.11 – 2.47, 0.014) (Table 3).

Table 3 Analysis of potential predictors of CKD in an at-risk population (uni- and multivariable results)

	Univariable		Multivariable	
	P-value	OR (95%CI)	Sig.	OR (95%CI)
Age (years)	0.003	1.05 (1.02 - 1.08)	0.001	1.06 (1.02-1.09)
Sex (reference (ref.): male)	0.194	0.79 (0.55 - 1.13)		
Arterial hypertension (ref.: no)	0.074	1.53 (0.96 - 2.46)		
Obesity (BMI > 30 kg/m²) (ref.: no)	0.059	1.44 (0.99 - 2.09)	0.033	1.55 (1.04-2.30)
Diabetes mellitus (Type 1 or Type 2) (ref.: no)	0.001	1.83 (1.27 - 2.64)	0.012	1.65 (1.12-2.43)
History of cardiovascular disease (reference: no)	0.945	1.02 (0.61 - 1.69)		
End-stage kidney disease in the family (ref.: no)	0.497	1.33 (0.59 - 3.01)		
Antihypertensive drugs	0.007	1.89 (1.19 - 2.99)		
Other long-term medications	0.014	1.65 (1.11 - 2.47)		
Statins	0.029	1.49 (1.04 - 2.14)		
Antidiabetic drugs	0.001	1.87 (1.30 - 2.68)		
Non-steroidal anti-rheumatic drugs (NSAR)	0.738	0.91 (0.51 - 1.61)		

Other variables with p <.2 were sex (higher risk for men), arterial hypertension and obesity. Higher age (OR 1.06, 95%CI: 1.02 – 1.09), diabetes mellitus (OR 1.65, 95%CI: 1.12 – 2.30) and obesity (OR: 1.55, 95%CI: 1.04 – 2.30) turned out to be independent significant predictors of previously undetected CKD in the multivariable analysis of the at-risk population.

4 Discussion

4.1 Summary

The nephrology awareness study “kidney.care 2.0” included 749 Austrian patients between 40 and 65 years of age and with one or more risk factors (hypertension, diabetes, cardiovascular disease, obesity or family history of end-stage kidney disease). The prevalence of previously undetected CKD was estimated at 20.1%. In a multivariate analysis, age, diabetes and obesity were independent predictors of CKD. Albuminuria (A2-A3) was present in the majority of patients with previously undetected CKD. Most patients with previously undetected eGFR < 60 ml/min/1.73 m^2 were in stage G3.

4.2 Comparison with existing literature

Our results confirm those of previous research that the prevalence of CKD in patients with additional risk factors such as arterial hypertension, diabetes, obesity, etc. (2, 5-8, 10, 13, 41-47) is high. However, in our multivariate analysis, only age, diabetes and obesity remained significant predictors. Although gender and arterial hypertension were not predictive of CKD in our study of over 700 patients, the odds ratios tended in the same direction as previous prevalence studies involving high number of patients that reported that female sex (6, 43, 44, 48, 49) and arterial hypertension (5, 6, 10, 41, 43, 47, 50) were both predictive of CKD, e.g. the systematic analysis for the Global Burden of Disease Study (49) or the National Health and Nutrition and the Examination Survey (47).

However, in the systematic review by Mills (51), there was no difference in CKD prevalence between females and males in younger age groups.
It is also unsurprising that age is an independent predictor of CKD (5, 6, 43, 52, 53), as was also seen in our study population of middle-aged patients. However, it should be taken into account that a decline of 6-7 ml/min/1.73 m^2 per decade from of the age of 35 to 40 years is part of normal ageing (54). It is therefore understandable that some researchers recommend adjusting the 60 ml/min/1.73 m^2 threshold according to age (55, 56). For example, in a UK study in which Shardlow et al. followed up on 1,741 patients with mild (stage G3) CKD in 32 GP practices, the majority had stable kidney function after 1 and 5 years, and only a very small minority developed end-stage kidney disease, with 18% showing a less severe progression after 5 years (57). The authors concluded that the intervention should focus on slowing the progression of CKD and reducing the number of cardiovascular events in a small group of patients at high risk of adverse outcomes. They therefore recommended an age-adjusted definition of CKD to avoid considering a large group of people with age-related decline in GFR as ill.
In our study population, obesity was an independent predictor of CKD, which is in agreement with other studies (8, 50). However, it remains unclear whether obesity in CKD patients is also associated with future cardiovascular diseases. One systematic review and meta-analysis of observational cohort studies and randomized controlled trials that included over 27,000 individuals without end-stage CKD provided evidence that obesity was not significantly associated with cardiovascular events (2).
Diabetes is a major risk factor in the development of CKD (5, 6, 10, 41-43, 46, 48) and is the leading cause of end-stage kidney disease (58). A recent study by Ohkuma showed that both decreases in eGFR and increases in ACR over 2 years, were significantly associated with a higher risk of myocardial infarction, stroke, cardiovascular death, major kidney events and all-cause mortality in patients with type 2 diabetes. The study results suggest that a combined assessment of clinically meaningful changes in both eGFR and ACR improves the risk stratification of people with type 2 diabetes with regard to their risk of experiencing major cardiovascular and kidney events (59).
In the “kidney.care 2.0” study, albuminuria was present in the majority of our patients with previously undetected CKD, which agrees with the results of previous screening studies in high-risk individuals (40-42). It is well known that predictive models for end-stage kidney diseases are significantly limited by a lack of external validity and efficacy (60). Nonetheless, the classification into different stages provides helpful guidance and supports communication with patients. In 2019, a new predictive model was adapted from the Kidney Failure Risk Equation (KFRE) (38) and published for the primary care setting (61). It is based on a British cohort and assesses more accurately the risk of end-stage kidney disease in primary care after 2 and 5 years, thus reducing the number of unnecessary referrals and increasing the number of earlier referrals in those at high risk of developing end-stage kidney disease (61). Even though most stage G3 CKD patients never progress to end-stage kidney disease, they are more likely to experience other adverse events such as those linked to cardiovascular diseases (1-3). Based on an adapted KFRE model that took into account cardiovascular comorbidities, the 5-year risk of progression to kidney failure in our patient group was stratified as high (62).

4.3 Screening and treatment strategies

Symptoms of CKD are often lacking and awareness of the disease is generally low, not only in primary care (12, 14, 18), but also in the hospital setting (14, 17, 63, 64). We therefore chose a pragmatic approach to screening in Austrian GP practices, which is the place where most asymptomatic patients with mild CKD are first identified. Unlike other countries, no database of electronic health records exists in the primary care setting in

Austria (13, 62, 65). In our study, patients we identified as at high risk were screened and their health care managed according to our adapted "kidney.care 2.0" program. The written materials provided in the training course recommend doctors ensure their patients undergo regular laboratory tests. They also recommend optimizing treatment by seeking close support from nephrologists via a telephone hotline, and through preferential access to the outpatient clinic responsible for monitoring progression. Similar procedures were also performed in other studies (20, 28) in which only high-risk patients were screened for CKD in a primary care setting because screening those with no risk factors was considered to be excessive (66). Furthermore, it is not only GPs that are unaware of the dangers of kidney disease but also the patients themselves. In a survey in the UK, it was shown that only one in two people knew that kidneys produce urine and only 12% of the population knew that kidneys play a role in processing medicines (67). Furthermore, Weckmann et al. (15) described in a German population cohort study that only 9% of participants with reduced GFR reported having CKD. Against this background, disclosure of kidney dysfunction to patients appears advisable in that it would probably encourage them to adhere to appropriate kidney protective therapies and life style modifications (exercise and diet), and raise their awareness of the need to both adjust doses of kidney excreted drugs and avoid nephrotoxic substances. Considering that a systematic review that included several educational interventions for patients with CKD has shown that, although inconsistent, different educational interventions lead to some improvement in patient reported and relevant outcomes, there would also appear to be a need for more patient education and information (68).

Although there is no robust evidence for the usefulness of screening and monitoring strategies for CKD (32, 69, 70), several guidelines (24, 71) and consensus statements (28, 72, 73) on screening and monitoring nonetheless exist. However, it should be borne in mind that over-testing can lead to harm through the incorrect labelling and reclassification of patients, as this may be associated with unnecessary changes in medications and possible additional costs (25). These uncertainties highlight the importance of shared decision-making between doctors and patients.

We implemented the "kidney.care 2.0" program because experience in various countries has shown that in primary care settings, full CKD screening and diagnosis/detection (i.e. assessment of both eGFR and ACR) is rarely routinely performed for at-risk patients (14, 18, 74). Several factors may help explain this, including a lack of awareness of the importance of early diagnosis of CKD among GPs (16). For this reason, the "kidney.care 2.0" program also aimed to increase awareness through educational interventions. In Styria, Austria, a further reason may be that the health care system does not foresee reimbursement of the cost of ACR testing. Similarly, resource constraints may mean that laboratories do not automatically, and GPs do not routinely calculate eGFR.

Currently, patients with CKD and/or albuminuria are generally prescribed ACE-Inhibitors or Angiotensin Receptor blockers (37). Studies like the RENAAL- study by Brenner showed that such standard care leads to a reduction in eGFR loss and slows the progression to end-stage kidney disease in patients with type 2 diabetes (67). In recent years, the armamentarium used in the treatment of CKD with or without albuminuria has been expanded through the use of the new sodium glucose transport 2 (SGLT2)-inhibitor. Several studies have shown that it dramatically slows the deterioration of kidney function in diabetic and non-diabetic patients, as well as having a very positive impact in patients with chronic heart failure (75). It is therefore of the utmost importance that CKD and/or albuminuria are identified at an early stage, as nephrologists now have a very effective means of treating CKD (76). Other drugs for the treatment of diabetic albuminuric kidney disease are in the pipeline (77), which are expected to further slow the progression of CKD, and lead to a dramatic reduction in cardiovascular events (67, 78).

The first part of the "kidney.care 2.0" study aimed to identify CKD patients at increased risk of primarily adverse cardiovascular outcomes and to support them with subsequent monitoring and targeted clinical management. It remains to be seen whether we will see a change in prescribing behavior and slower progression to CKD in this patient population (33) in the 12-month follow-up period.

4.4 Strengths and limitations

The "kidney.care" project was launched in 2016 (30) and has implemented several initiatives aimed at increasing awareness of the importance of screening in the primary care setting. The "kidney.care 2.0" program was launched in 2021 and has attempted to increase awareness through updated training courses, further education via public media, and on-site visits to GPs. In a previous publication, various evaluation methods for the awareness program "kidney.care" were discussed and we came to the conclusion that it should be embedded in a disease management program, which does not yet exist in Austria (32). In addition, unlike the UK (79), the USA (80) and Canada (20), no large-scale national societies and initiatives exist.

Even though risk factors such as hypertension, a history of cardiovascular diseases and a family history of end-stage kidney disease have been shown to be predictors in several prevalence studies (2, 5, 6, 10, 41, 43, 47, 50, 81, 82), we could not provide similar evidence in our study population (33), which may be due to its small size.

As part of "kidney.care 2.0", only one laboratory test was carried out to determine CKD on the basis of a reduced eGFR and an elevated albumin-creatinine ratio (ACR), with a further measurement of ACR not being undertaken until three months later in case of first-time albuminuria. It was therefore impossible to draw a conclusion on the permanence of impaired kidney function. Furthermore, overdiagnosis cannot be ruled out as it is unclear to what extent the lack of repeated measurements of eGFR may have affected the result. Another reason for a potential overestimate might be the biological and analytical variability of eGFR and ACR (71). Therefore, the planned follow-up survey will determine whether the CKD cases detected at baseline can be reconfirmed. This analysis will help to distinguish persistent CKD cases from those influenced by transient variations in kidney function and albuminuria.

A further limitation of the present study is that eGFR was calculated using the 2009 Epidemiology Collaboration (CKD-EPI) equation (36) rather than the updated CKD-EPI equation published in 2021 (83). This discrepancy may affect the comparability of our study results with other publications.

It should be noted that one of this study's limitations is that when the "kidney.care" program was developed in 2016, we restricted patient inclusion to predefined risk groups in accordance with NICE Guidelines (84). We later decided to further restrict the program to include only middle-aged patients because of such practical considerations as the feasibility of the program for GPs and the availability of funding. In view of the continued implementation of the "kidney.care" program, it is imperative to assess the necessity to adapt the risk groups to be screened for CKD in accordance with the current KDIGO Guideline 2024 (71). Risk groups would then include, for example, patients with previous acute kidney injury, chronic inflammation and younger diabetic patients.

In our referral recommendations, we suggest implementing specific monitoring intervals, especially for those in whom CKD has not yet been detected. Our recommendations are based on consensus papers (85, 86) and the opinion of nephrology experts. However, as no high-quality studies have addressed the optimal frequency for testing patients with (or at high risk of developing) CKD, harm from over-testing cannot be ruled out (25, 69). While this may be a challenge for screening programs outside a trial setting, regular monitoring has clear advantages and is essential in a study context, particularly for the reliable

detection of changes in renal function and the onset of CKD. Papers by Major (61) and Mosa (62) had not been published when our referral recommendations were adapted from the KFRE (38). It is possible that our recommendations will be adjusted to take account of the findings reported in these publications.
The Covid pandemic often made GPs unwilling to participate, which slowed down the recruitment of patients considerably. A further limitation of our study is that the sample of participating GPs was not representative.
Despite several extensions to the recruitment period and local support measures on-site, it became apparent in spring 2022 that the target of including 1,000 patients would not be reached. For this reason, the sample size calculation was carried out again in April 2022. The calculation revealed that a reduction to 700 patients would decrease precision from ±2.5 to ±4.2 to ±3.1 to ±5.1. This was considered acceptable.
In order to account for the effects on the results of differences between individual practices, a random effect was included in the statistical analysis. However, no systematic analysis of the influence of specific participating practices on the results was conducted. Furthermore, no systematic investigation into the socioeconomic characteristics of study participants and their influence on the results was performed. These factors could be subjects for further investigation in future studies. It is also important to note that the limited scope of the study meant that the study population was not as diverse as would have been desirable in terms of ethnicity.

4.5 Implications for research and/or practice

The aim of our study was to integrate pragmatic CKD screening into the routine workflows of GP practices and to raise awareness among GPs of the need for regular follow-up care of CKD patients. As this study was carried out in only one federal state of Austria, the next step is to implement it on a national scale, as was recommended when the Austrian periodic health examination was revised in 2019 (87). The European Society of Cardiology (ESC) Guideline 2021 on Cardiovascular Disease Prevention in Clinical Practice 2021 also proposes a cardiovascular risk assessment in at-risk individuals and even considers a systematic or opportunistic cardiovascular risk assessment in men aged >40 years and postmenopausal women or women >50 years (88). The Council of the European Renal Association recommends that a cardiovascular risk assessment in the general population should include the assessment of eGFR und ACR (89).
In addition, with the support of the Austrian Society of Nephrology (90) and the Austrian Society of General Practice and Family Medicine (91), we will further sensitize GPs to the necessity of keeping a close eye on people at increased risk of CKD, as most patients with CKD can be managed in a primary care setting, as long as the option of referrals to nephrologists or of contacting nephrologists is also available. The “kidney.care 2.0” program is a perfect basis on which to expand existing cooperation.
Future research should investigate the efficacy of CKD screening program on patient-relevant clinical outcomes. This is why the U.S. Preventive Services task force (USPSTF) is planning a systematic review of the effects of screening for CKD in order to update its recommendations. A key question is the effect of screening for CKD versus no screening on clinical outcomes in asymptomatic adults without known CKD (92).

5 Conclusion

In this milestone Austrian study, pragmatic, risk-based, targeted screening for CKD in primary care was able to identify a large number of patients with previously undetected

CKD. Further research should be conducted to find out whether risk-based, targeted screening and subsequent monitoring for CKD in primary care has the potential to optimize the care of middle-aged patients, slow the progression to kidney failure, and prevent cardiovascular events.

6 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

7 Author Contributions

ASK: conceptualization, funding acquisition, methodology, project administration, supervision, writing – original draft. CL: conceptualization, data curation, investigation, methodology, project administration, resources, writing – original draft. AA: conceptualization, data curation, formal analysis, methodology, validation, writing – original draft. EP: conceptualization, data curation, investigation, methodology, project administration, resources, writing – review and editing. CZ: conceptualization, data curation, investigation, methodology, project administration, resources, writing – review and editing. AM: conceptualization, data curation, methodology, resources, writing – review and editing. USK: conceptualization, methodology, writing – review and editing. AB: conceptualization, data curation, formal analysis, methodology, project administration, supervision, validation, writing – review and editing. AR: conceptualization, funding acquisition, methodology, project administration, supervision, writing – original draft. All authors contributed to the article and approved the submitted version.

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11 Data Availability Statement

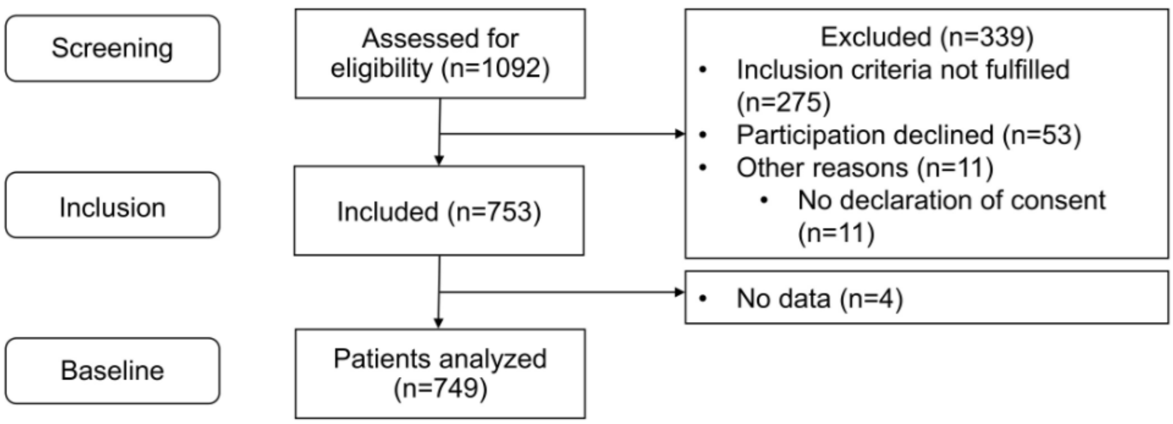
The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Figure 1: kidney-care referral schema

eGFR ml/min/1.73 m² \ Albuminuria mg/g	A1 < 30	A2 30 – 300	A3 > 300
≥ 60	1 x annual laboratory check by general practitioner incl. risk factor optimization	eGFR stable: 1x annual check-up in the outpatient setting incl. risk factor optimization eGFR loss ≥ 10 per year: Check-up by nephrological progression outpatient clinic or nephrologist	Check-up by nephrological progression outpatient clinic or nephrologist
30 – 59	eGFR stable: 1x annual check-up in the outpatient setting incl. risk factor optimization eGFR loss ≥ 10 per year: Check-up by nephrological progression outpatient clinic or nephrologist	eGFR stable: 2x annual check-up in the outpatient setting incl. risk factor optimization eGFR loss ≥ 10 per year: Check-up by nephrological progression outpatient clinic or nephrologist	Check-up by nephrological progression outpatient clinic or nephrologist
20 – 29	Check-up by nephrological progression outpatient clinic or nephrologist	Check-up by nephrological progression outpatient clinic or nephrologist	Check-up by nephrological progression outpatient clinic or nephrologist
< 20	Admission to nephrological reference center: collaborative care	Admission to nephrological reference center: collaborative care	Admission to nephrological reference center: collaborative care

Version 3.0 11/2020

Figure 2: patient flow chart



12 Supplementary Tables

Supplementary Table 1. Detailed description of recruitment and screening

General practitioner recruitment	In order to obtain the requisite number of 30 to 40 collaborating GPs, a variety of recruitment measures were implemented between January 2021 and November 2022. Recruitment was conducted by sending by out a written invitation by e-mail or post to all Styrian GPs under contract to the biggest Statutory Austrian Health Insurance Fund (Österreichische Gesundheitskasse), to all GPs that are members of the Styrian Society of General Practice and Family Medicine, and to about 110 GPs listed in the research network of our Institute of General Practice and Evidence-based Health Services Research. In addition, our study was presented at regional medical training events and congresses for general practitioners (GPs). Information about the content of the study was further disseminated via relevant Austrian healthcare journals.
Screening and patient recruitment process	To avoid selection bias, we aimed to consecutively screen all at-risk patients aged 45 to 65 years that attended a particular practice during an eight-week period until 24 to 40 eligible patients had been identified. GPs could choose when the eight-week period best suited them as along as it was between January 1, 2021 and December 31, 2022. Due to the Covid-19 pandemic, it was possible for GPs to extend the eight-week period in agreement with the study team.
Screening list	Each GP received a screening list on which to record details of all screened patients, including the date of screening, patient screening number, first and last names, date of birth, and the final decision on their inclusion or exclusion from the study. To ensure data privacy, the screening list remained in the participating GP practices.
Screening questionnaire and written informed consent	To check patient’s eligibility, a screening questionnaire was completed by the GP. This included the date of screening, GPs’ study ID, the patient’s screening number, age, sex, and the study's inclusion and exclusion criteria. Eligible patients were invited to participate in the study “kidney.care 2.0” during their doctor-patient consultations. If a patient agreed to participate in the study, written informed consent was obtained.

Supplementary Table 2. Characteristics of patients with CKD compared to patients without CKD

Patient characteristics (number of patients with available data)		Total	*CKD* *No*	*CKD* *Yes*	*p-value*
Sex (n=749)	male	404 (53,94%)	316 (52,8%)	88 (58,7%)	.203
	female	345 (46,06%)	283 (47,2%)	62 (41,3%)	
Age Groups (n=749)	40 - <50	138 (18,42%)	119 (19,9%)	19 (12,7%)	.044
	50 - <60	357 (47,66%)	287 (47,9%)	70 (46,7%)	
	60 - <70	254 (33,91%)	193 (32,2%)	61 (40,7%)	
Diabetes mellitus (Type 1 or Type 2) (n=740)	No	409 (55,27%)	345 (58,3%)	64 (43,2%)	.001
	Yes	331 (44,73%)	247 (41,7%)	84 (56,8%)	
Arterial hypertension (at least 3 months >140/90mmHg) (n=736)	No	167 (22,69%)	142 (24,1%)	25 (17,1%)	.065
	Yes	569 (77,31%)	448 (75,9%)	121 (82,9%)	
Obesity (BMI >30 kg/m²) (n=722)	No	343 (47,51%)	287 (49,2%)	56 (40,3%)	.082
	Yes	379 (52,49%)	296 (50,8%)	83 (59,7%)	
History of cardiovascular disease (n=739)	No	629 (85,12%)	505 (85,2%)	124 (84,9%)	.926
	Yes	110 (14,88%)	88 (14,8%)	22 (15,1%)	
End-stage kidney disease in the familiy (n=723)	No	690 (95,44%)	556 (95.7%)	134 (94.4%)	.450
	Yes	33 (4,56%)	25 (4.3%)	8 (5.6%)	
Antihypertensive drugs (n=746)	No	195 (26,14%)	169 (28,4%)	26 (17,3%)	.005
	Yes	551 (73,86%)	427 (71,6%)	124 (82,7%)	
Statins (n=745)	No	441 (59,19%)	364 (61,2%)	77 (51,3%)	.032
	Yes	304 (40,81%)	231 (38,8%)	73 (48,7%)	
Non-steroidal anti-rheumatic drugs (NSAIDs) (n=733)	No	648 (88,40%)	516 (88,2%)	132 (88,4%)	.694

	Yes	85 (11,60%)	69 (11,8%)	16 (10,8%)	
Antidiabetic drugs (n=741)	No	460 (62,08%)	385 (65,1%)	75 (50,0%)	<.001
	Yes	281 (37,92%)	206 (34,9%)	75 (50,0%)	
Other long-term medication (n=739)	No	257 (34,78%)	218 (36,9%)	39 (26,2%)	.011
	Yes	482 (65,22%)	372 (63,1%)	110 (73,8%)	

Anhang 2: Kommentare der Reviewer und deren Beantwortung

Reply to authors – revision 1 (2024-06-23)

Comments of Reviewer 1

Dear Reviewer,

We sincerely appreciate your thorough review of our manuscript. Your insightful comments have certainly contributed to improving the quality of our paper. We have taken all your suggestions into consideration and have revised the manuscript in accordance with each of the points you raised.

Best regards!

Comment 1: I understand that you focused your research on the middle-aged group but I believe that all these comorbidities tend epidemiologically to appear at younger ages and with patients getting still repeated COVID infections we should expect an increase in CKD cases among patients younger than 40. My point is that younger patients are in great need for screening as well and this should be discussed or added as another limitation.

Thank you for your comment, which we completely agree with. However, practical considerations (e.g. the feasibility of the study for GPs and the availability of funding) meant we had no option but to limit the inclusion of patients to predefined middle-age risk groups. We now discuss this in our comments on limitations on lines 351 to 358.

Comment 2: Would comment in the introduction or the discussion that not only GPs ignore CKD in their practice but also other subspecialties: endocrinologists, cardiologists, oncologists, rheumatologists.

The issue of undiagnosed CKD in the presence of pertinent laboratory markers such as eGFR and ACR in other clinical contexts has already been addressed in lines 62 and 65 of the introduction by a paper published by Friedl et al.. This crucial point has also been addressed in lines 276 to 277 of the discussion section.

Comment 3: Another suggestion is to discuss briefly other conditions that may lead to CKD even beyond the traditional comorbidities. It is easy for example to test for chronic inflammation. A Hx of previous AKI or ICU hospitalization etc.

Thank you for your comment. As mentioned above, it is unfortunately the case that practical considerations (e.g., the feasibility of the study for GPs and the availability of funding) meant we had no option but to limit the inclusion of patients to predefined middle-aged risk groups. We now discuss this in our comments on limitations on lines 351 to 358.

Comment 4: Line 47: I would not exactly say 'undetected', since laboratory evidence means it is detected. Maybe under-reported/under-estimated/under-diagnosed?

Your are right of course! We have now adjusted the text accordingly, which now reads "undiagnosed" rather than "undetected."

Comment 5: In addition to the fact that many GPs do not wish to lose their 'clients' and thus do not refer in a timely manner (but this is difficult to discuss), you could comment on the fact that many practitioners rely only on SCr and do not calculate correctly eGFR (when not provided by the lab). Also, even if the SCr is normal or the eGFR>60 many do not check for albuminuria or microalbuminuria even with traditional risk factors being present.

The nephrologists involved in our study agree wholeheartedly with all of your points. As your first point is challenging to discuss, we have decided not to comment on it in our manuscript. As far as

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your second point is concerned, we believe there are multiple reasons why eGFR and ACR are not checked in a GP setting. We now address this point on lines 307 to 314 of the discussion.

Comment 6: What exactly do you mean in line 97 by 'ethical groups'?

Thank you for noticing our mistake! We intended to write "ethnic groups" - use of the term "ethical groups" was a typographical error. We have now corrected the error in line 110 of the manuscript.

Comment 7: Please explain why you excluded cancer and HF stage II pts?

Cancer patients were excluded from the present study because tumor-specific therapies are often nephrotoxic. Pain treatment in cancer patients also tends to include the administration of nonsteroidal anti-inflammatory drugs (NSAIDs), which are also nephrotoxic. Furthermore, cancer patients are subject to fluctuations in hydration status during their treatment, which can also affect kidney function.

Thank you for bringing this typographical error to our attention! It was never our intention to exclude heart failure stage II patients from our study. As you can see in the German Clinical Trials Register https://drks.de/search/en/trial/DRKS00022966, heart failure patients > NYHA II were excluded. We have corrected line 116 of the manuscript accordingly.

Comment 8: As a next step it would be interesting to explore GP practice characteristics (years of expertise, size of the practice, location, insurance acceptance, etc.) and socioeconomic characteristics of CKD pts that may influence CKD diagnosis.

Finally, another limitation is that your patient population is of the same ethnicity and race.

Thank you for your comment. We completely agree! In order to account for the effects of the differences between the participating practices on the results, we included a random effect in the statistical analysis (lines 172 to 177). However, we neither conducted a systematic analysis of the possible influence of individual practices on the results, nor of the socioeconomic characteristics of study participants and their influence on the results.

We now explicitly state in the limitations section of the manuscript that the relatively narrow scope of the study meant the trial population was not as diverse as we would have liked in terms of ethnicity . These points have been mentioned in the discussion section on limitation (lines 378 to 384).

Comments of Reviewer 2

Dear Reviewer,

We sincerely appreciate your thorough review of our manuscript and thank you very much that you have drawn our attention to some further papers. Your insightful comments have certainly contributed to improving the quality of our paper. We have taken all your suggestions into consideration and have revised the manuscript in accordance with each of the points you raised.

Best regards!

Comment: Line 51 You should make a distinction between diagnosis and coding. CKD is mostly not the leading medical problem an is therefor not coded., which does not mean it is not noticed.

Thank you for pointing this out. We've added more detail in lines 51 to 52 of the text. Please also see our answer to the comment below.

Comment: Please see regarding coding of CKD
Weckmann G, et al. Monitoring and management of chronic kidney disease in ambulatory care - analysis of clinical and claims data from a population-based study. BMC Health Serv Res. 2022 Nov 9;22(1):1330.

Thank you very much for this important comment. In addition to pointing out that there are a number of reasons why CKD often remains uncoded, we are happy to consider Weckmann's paper in our study, not only because it provides further proof of a discrepancy between CKD coding and laboratory evidence of CKD, but also because it strengthens the evidence that only a small number of patients were aware that a pathological laboratory result had shown that they had CKD (see line 53 and line 55). In addition, we now include in our introduction section a systematic review dealing with barriers and enablers to the detection and management of CKD in primary healthcare (Neale, BMC Nephrology 2020) (see line 56 to 62).

Comment: Information on the representativeness of participating GPs is missing an how they were approached is missing.

We are grateful for this comment. To ensure widespread recruitment and to reach the predefined number of GPs, we employed multiple recruitment strategies. We have mentioned the multiple recruitment strategies now into the newly inserted chapter 2.2 "Recruitment and screening" on lines 131 to 132. A detailed description of these strategies is now presented in the newly inserted Supplementary Table S1. Unfortunately, our sample of participating GPS was not representative. We have added this point in the study limitations section on lines 371 to 372.

Comment: Line 118. Further information how GPs invited patients to participate in the screening is needed.

Thank you very much for this comment. A description of how GPs invited patients to participate in the study is now provided in the newly inserted chapter 2.2 "Recruitment and screening" on lines 132 to 138. A detailed description of the screening is now presented in the newly inserted Supplementary Table S1.

Comment: Overall, the process how patients where approached needs to be described in more detail.

Thank you very much for your comment. Please refer to the newly inserted chapter 2.2, "Recruitment and screening", on lines 130 to 138 of the methods sections, and the Supplementary Table S1 for a detailed description of how patients were approached.

Comment: You state the primary aim was to identify previously undetected CKD. It is not described how patients with previously detected CKD where excluded. How is diagnosis coded in Austrian? ICD 10?

We had to rely on the documentation provided by GPs, whereby the presence of renal insufficiency was determined by the GPs on the basis of their patient records. In Austria, there is no mandatory diagnostic coding system in primary care. For your personal information, in January 2023, a law was finally passed that will mandate coding in primary care as of 2026.

Comment: How did GPs know about family history of CKD. Is this regularly documented in Austria?

In Austria, it is common for such information to be obtained verbally during patient consultations. It is essential to emphasize that data protection legislation means access to this information by third parties is not permitted.

Comment: It is not described how many patients between 40- and 65-years patients where eligible for screening in all practices., e.g. by extraction of all listed patients from the electronical medical records. The patient flow chart showing all patients eligible, all patients excluded, all patients contacted and all patients who participated is incomplete. It in is unlikely that 33 GPS have only 1092 patients between 40- and 65-years. It seems most patients where not contacted.

No pre-screening of medical records was undertaken. Instead, general practitioners assessed eligibility and approached potential participants for study recruitment during routine practice visits conducted over an 8-week period. We opted for this consecutive screening approach to mitigate the risk of selection bias. As mentioned in lines 369 to 371 of the discussion section, the COVID-19 pandemic presented unforeseen challenges to patient recruitment. The extraordinary demands placed on GPs during this period limited their capacity to participate as initially anticipated.

Comment: A range of how many patients where included from each practice would be helpful. This would be an important information to draw conclusions on the representativity of the sample and possible selection bias.

Thank you very much for you comment. The requested information on the number of patients included per GP practice has been added and can now be found (see lines 189 to 190).

Comment: Figure 1
Why should somebody with an eGFR > 60 and no albuminuria have annual monitoring of the Kidney function? What is the rationale? The evidence for screening is low (see your introduction) and the evidence for monitoring intervals even lower.
Elwenspoek MMC, Patel R, Watson JC, Whiting P. Are guidelines for monitoring chronic disease in primary care evidence based? BMJ. 2019 Jun 13;365:l2319.

It is true that evidence for the benefits of screening and monitoring is weak, and consequently it is not recommended in evidence-based guidelines. Furthermore, when the “kidney.care program“ was designed in 2016, hardly any national or international guidelines on CKD screening were available. Our rationale for annually monitoring patients with an eGFR > 60 and no albuminuria was based firstly on consensus papers written by international nephrology experts that were drawn to our attention by the nephrologists that participated in our study, and secondly, the pragmatic requirement to facilitate the achievement of the study objective to have a 12-month follow-up

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examination. We have now added this information on lines 301 to 306 of the discussion and line 359 to 368 of the limitations section now.

Comment: Figure 3
The data shown in figure 3 is already given in table 3.

Thank you very much for your comment. We have deleted figure 3 in the actual version of the manuscript.

Comment: It is unfortunate that the newly detected patients are not described in more detail and how the newly established diagnosis of CKD lead to clinical implications.

A description of newly detected patients has now been added and can be found on lines 194 to 197. The intended clinical implications (risk factor optimization, referral to nephrologist, etc.) for newly detected CKD cases are specified in the referral graphic (Figure 1). The extent to which these were implemented by participating GPs will be analyzed in the planned follow-up survey.

Comment: Overall, the conclusion regarding the utility of screening seems to strong. This is an epidemiological study which did not demonstrate any benefits on clinical outcomes.

We would like to thank you for your valuable input and agree that the conclusions we draw should be tempered. In response to your comments, we have revised our conclusions in the "Conclusion" section (lines 409 to 414). Furthermore, we have weakened the concluding statement in the abstract (line 38).

Anhang 3: Kommentare des Editors und deren Beantwortung

Reply to the editor (2024-07-23)

Comments of the editor

Dear Authors,

Thank you for this manuscript, which addresses an important public health issue, and your response to the reviewers' comments.

A few comments before a final decision is taken:
1. Do you not consider that a CKD prevalence of 20.1% (even in at-risk populations) is an overestimate? Especially when we consider that most of the "CKD" patients had eGFR in the 45 to 60ml/min/1.73m2 range, and albuminuria (maybe transient) was the main driver of this high estimate. Is it possible to report what proportion of the patients with albuminuria had sustained albuminuria at the 12-month visit? What proportion of those with eGFR < 60ml/min at initial screening had sustained low eGFR at 12 months?

2. A major limitation of this work is the use of the outdated CKD-EPI 2009 equation when we had an updated CKD-EPI equation published in 2021 (N Engl J Med
. 2021 Nov 4;385(19):1737-1749. doi: 10.1056/NEJMoa2102953). Is it possible to compute the CKD prevalence using the new CKD-EPI equation and present it as supplementary data?

Thank you.

Comment 1:

Thank you for your comment. Our results are in line with other studies (lines 218 to 219) , so we believe that the observed prevalence is not an overestimate. However, we agree with your point regarding the stability of diagnostic parameters and have mentioned the biological and analytical variability of eGFR and ACR as a further argument for potential overestimation in the discussion section on lines 340 to 341.

At this time, data from the 12-month follow-up survey are not yet available. This is a baseline publication but it is planned to conduct such an analysis in a subsequent publication. In our manuscript, we now refer to the planned analyses in lines 341 to 344 of the discussion section.

Comment 2:

Thank you for your comment. Unfortunately, it is not possible to compute the CKD prevalence using the new CKD-EPI 2021 equation. In our case report form , only eGFR and not serum creatinine was documented, making it impossible to re-calculate the results using the updated CKD-EPI equation published in 2021 within this study. We have now acknowledged this as a further limitation of our study (see lines 345 to 347).

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Anhang 4: Darstellung des eigenen Anteils

Die Masterarbeit umfasste die Erstellung des Publikationsmanuskripts, wobei die Details für die Leistungen sämtlicher Personen in dieser Tabelle dargelegt werden.

	Siebenhofer	Loder	Avian	Platzer	Zipp	Mauric	Spary-Kainz	Berghold	Rosenkranz
Entwicklung des Konzeptes für den Aufbau des Manuskripts	vollständig								
Erweiterte Literaturrecherche für das Manuskript	in Teilen	in Teilen							
Aufbereitung des Hintergrundes	vollständig								
Darstellung der Methodik	in Teilen	in Teilen							
Interpretation der Datenauswertung im Ergebnisteil	überwiegend	in Teilen	überwiegend					in Teilen	
Diskussion	überwiegend	in Teilen							in Teilen
Kritische Durchsicht des Manuskriptes	ja	ja	ja	ja	ja	ja	ja	ja	ja
Einarbeitung des Feedbacks	in Teilen	in Teilen	in Teilen						
Bearbeitung der Reviewerkommentare	überwiegend	überwiegend	in Teilen						in Teilen

Tabelle: Leistungen weiterer Personen für die Verfassung des Manuskripts.