

**Health Care and Social Networks in the Context
of Neurodegeneration and Mortality in Old Age and End of Life**

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Summary

The demographic trend in Germany is characterized by decreasing birth rates and a continuous increase in life expectancy. The number of people over the age of 85 will rise from 1.1 million in 1990 to 2.5 million in 2020 and is expected to at least double again over the next five decades. Age-related diseases, particularly neurodegenerative conditions such as dementia, are becoming more prevalent. A considerable increase in the number of people with dementia is predicted; by 2050, the total number of people with dementia is expected to reach 2.8 million. The lack of a cure combined with the increase in multimorbidity will lead to an increase in the number of people in need of health care and the demand for care. Around 90% of people with dementia will require health care during the course of their illness, making dementia one of the main causes of the need for long-term care. At the same time, demographic change is also reflected in the context of the care environment. The demographic trend, which manifests itself in a decrease in the number of people in middle age, results in a reduction in potential caregivers. For this reason, social networks and social participation are becoming increasingly important for older adults.

The intention of this thesis is to analyze the influencing factors of care, social networks and cognition in the context of health and mortality in old age. As part of this, relevant risk and protective factors in the course of dementia are analyzed and evaluated. In addition, existing care measures will be examined for effectiveness and appropriateness in the context of current care needs in order to identify potential gaps in care.

This thesis comprises three studies that examine health from two different perspectives: the pathogenetic approach and the salutogenetic approach. The individual studies in this thesis focus on different aspects of the disablement process of dementia, starting from a healthy cognitive state through the development of pathology, impairments and functional limitations to death.

Study I investigated the association between sporadic use of antibiotics for systemic use and subsequent dementia risk in old age. The study was conducted using health claims data from the Allgemeine Ortskrankenkasse health insurance fund for the period from 2006 to 2018. The analysis included people who were at least 60 years old at the start of the observation period. The results of the study suggested that antibiotics for systemic use can reduce the progression of infectious inflammation and thus slow the progression to clinically manifest dementia symptoms.

Study II examined the factors that influence the risk of a palliative care prescription. It also identified established and unknown risk or protective factors associated with palliative care prescriptions. The factors were identified using the health claims data of the Allgemeine Ortskrankenkasse from 2014 to 2019 for people aged 50 years and older. The study highlights that, in addition to known predictors for

palliative care such as a cancer diagnosis, previously unknown factors such as a dementia diagnosis were also important predictors. However, dementia patients have a significantly lower probability of being prescribed palliative care compared to cancer patients.

Study III was dedicated to investigating the influence of social networks on the relationship between cognition and mortality in old age. For this study, data from participants of the German National Cohort (NAKO) aged 60 years and older were used, as well as the corresponding mortality follow-up. These data were collected as part of the baseline survey from 2014 to 2019. The finding of a U-shaped risk pattern in the interactions of cognition and social network on mortality risk suggested that moderate social integration may be particularly beneficial for individuals.

This thesis emphasizes the importance of regularly evaluating and reassessing risk and protective factors throughout the progression of dementia. It became evident that a reassessment of potentially known modifiable risk factors is essential to enable a weighing of benefit and risk in the context of other factors. Analyzing and evaluating the current state of care is essential to improving medical care for previously underrepresented patient groups. Understanding risk and protective factors, access to care, and social integration can positively impact successful aging and provide new approaches to care in old age.

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List of Abbreviations

AOK - Allgemeinen Ortskrankenkassen

ApoE - Apolipoprotein E

ATC - Anatomical Therapeutic Chemical Classification

BMI - Body Mass Index

HR - Hazard Ratio

ICD-10 - 10th revision of the International Classification of Diseases

MRI - Magnetic resonance imaging

NAKO - German National Cohort

OR - Odds Ratio

SGB - Code of Social Law

WiDO - Scientific Institute of the AOK

95% CI - 95% Confidence Interval

List of Original Publications

Study I:

Rakuša, E.; Fink, A.; Tamgüney, G.; Heneka, M. T. & Doblhammer G. (2023): Sporadic Use of Antibiotics in Older Adults and the Risk of Dementia: A Nested Case–Control Study Based on German Health Claims Data. *Journal of Alzheimer’s Disease* 93 (2023) 1329–1339. doi: 10.3233/JAD-221153

Study II:

Rakuša, E.; Reinke, C.; Doblhammer, G.; Radbruch, L.; Schmid, M.; Welchowski, T. (2025): Dementia as a predictor of palliative care: Uncovering patient patterns based on German claims data. *BMC Palliat Care* 24, 46 (2025). doi: 10.1186/s12904-025-01672-y

Study III:

Rakuša, E.; Georges, D.; NAKO Consortium; Doblhammer, G. (2025): Exploring the Impact of Social Networks and Cognitive Function on Mortality in Older Adults: Insights from the German National Cohort (NAKO).

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1. Introduction

The demographic trend in Germany is characterized by decreasing birth rates and constantly increasing life expectancy (Robert Koch Institut, 2024; Walther, 2000). In the last 30 years, life expectancy at the age of 65 has increased from 18.0 to 20.8 years for women and from 14.3 to 17.5 years for men (Statistisches Bundesamt [DESTATIS], 2024a, 2025b). As a result, more and more people are reaching advanced age, with the number of people aged 65 and older rising from 12 million in 1991 to 18.7 million in 2022, and it is expected to grow again to 23.4 million over the next four decades (DESTATIS, 2023d, 2025c).

These demographic shifts are leading to an aging population (Walther, 2000). In particular, the very old aged 85 and older represent a rapidly growing group, and are associated with an increase in morbidity in the population. Age-related diseases, in particular neurodegenerative diseases such as dementia, are on the rise (Blotenberg et al., 2023; GBD 2019 Dementia Forecasting Collaborators, 2022).

In 2021, around 1.8 million people in Germany were affected by dementia, and the number of dementia patients will continue to rise rapidly; it is expected that by 2050, around 2.8 million people will be living with dementia (Alzheimer Europe, 2020; Deutsche Alzheimer Gesellschaft e. V.). Over 50% of very old people will have dementia at the time of death (Doblhammer & Barth, 2018), and forecasts show that by 2060, dementia could be one of the most common existing condition at the time of death (Doblhammer et al., 2022).

The absence of a curable dementia diagnosis, in combination with the increase in multimorbidity, will lead to an increase in the number of people in need of care and the demand for care (DESTATIS, 2023b). Around 90% of dementia patients require care at some point during the course of their illness, making dementia one of the main causes of the need for care (Laporte Uribe et al., 2017). At the same time, demographic change also affects the care environment. The decreasing number of middle-aged people results in a decline in the number of potential caregiving relatives. In this context, social networks and social participation are becoming increasingly relevant. A higher level of social participation can reduce the risk of cognitive impairment in older people (Barnes et al., 2004). Social networks can provide access to additional resources and improve well-being.

The German S3 Dementia Guidelines (DGN e. V. & DGPPN e. V., 2023) provide up-to-date recommendations for the prevention, diagnosis and treatment of dementia, as well as for advice and care for people with dementia. They provide the latest framework for appropriate health care in the German health system. However, there are gaps in end-of-life care. The end-of-life stage of people with dementia has not been explicitly addressed so far (DGN e. V. & DGPPN e. V., 2023), although the

progressive course of the disease inevitably leads to physical and psychological decline and a foreseeable transition to death (World Health Organization, 2023a).

One of the greatest challenges in dealing with demographic change and the increase in the number of older people is to identify the protective factors, risk factors and the mechanisms that are responsible for these individual differences in cognitive decline.

The aim of this work is to examine the influences of health care, social networks and cognition in the context of health and mortality. To this end, relevant risk and protective factors in the course of dementia will be researched, evaluated and reclassified. In addition, existing care measures will be examined with regard to their effectiveness and appropriateness in the context of current care needs in order to identify potential gaps in health care.

Study I investigated the influence of prescriptions of antibiotics for systemic use (in the following: antibiotic use) on the subsequent risk of dementia in older individuals. The aim was to re-evaluate known influencing factors in the context of potentially preventable risks in older ages. The benefits and risks of factors classified as risks (antibiotics for systemic use) are examined and unknown side and long-term effects are identified. The research question in study I is:

Is there an association between prescription of antibiotics for systemic use and subsequent risk of dementia?

The topic of dependency on care and the need for adequate care at the end of life is not considered in the present S3 guidelines. At this point, Study II addressed a gap and examined factors for the risk of a palliative care prescription. In addition, it contributed to the identification of established and unknown risk or protective factors associated with palliative care prescriptions:

- 1. Which factors are important predictors of the utilization of palliative care in older people?*
- 2. How do predictors influence the probability of receiving palliative care?*

The focus of the S3 guideline is on the medical field and does not include social networks and social support for patients (DGN e. V. & DGPPN e. V., 2023). Study III was dedicated to precisely this aspect in order to examine the influence of social networks on the relationship between cognition and mortality in older individuals:

- 1. Does the presence of a strong social network further reduce the mortality risk associated with cognitive performance?*

2. Does the combined effect of cognitive performance and social network integration on mortality vary across different cognitive domains?

Outline

The present thesis is divided into nine chapters and is based on three quantitative studies. After the introduction, Chapter 2 follows, which highlights health care in Germany. The German healthcare system as well as care outside the healthcare system are discussed. In addition, the level of care for dementia patients in Germany is described. Chapter 3 presents the theoretical framework of this work, in which the concept of health is analyzed from various perspectives. The chapter continues with a presentation of Andersen's behavioral model of the utilization of health services. The disablement process is introduced as a framework for the progression of dementia, and the three studies are placed in the context of the theoretical framework. The distinction between old age and the end of life is explained at the end of the chapter. Definitions of cognition and dementia are presented in Chapter 4, while in Chapter 5, the relevant risk factors for cognitive impairment and dementia are summarized. Chapters 6 and 7 offer a summary of the materials and methods used, as well as the main findings of each study. Chapter 8 discusses these findings in the broader context of the theoretical framework. Conclusions are drawn in Chapter 9.

2. Health Care in Germany

The following chapter presents the German healthcare system, including outpatient and inpatient care. It also briefly discusses the regulation of medications in Germany and the regulation of palliative care. After that, the section presents care outside of the healthcare system and concludes with the current state of care for dementia patients in Germany.

2.1. Healthcare System in Germany

The German healthcare system is one of the most well-organized health systems worldwide and is based on the principle of the social market economy, which ensures that every citizen has access to health care and free treatment (Bundesministerium für Gesundheit, 2022). This can be provided by statutory health insurance or private health insurance. The German healthcare system is based on five basic principles: compulsory insurance, the principle of solidarity, contribution-based financing, the principle of benefits in kind, and the principle of self-administration (Bundesministerium für Gesundheit, 2022; SGB V, 2024). Since the introduction of compulsory insurance, all citizens whose permanent place of residence is in Germany are obliged to have health insurance in order to be covered in the event of illness (§ 5 SGB V, 2024).

“Health insurance, as a solidarity-based community, has the task of maintaining, restoring, or improving the health of the insured [...] by providing information, advice and services [...]” (§ 1 SGB V, 2024). Everyone with statutory health insurance has the same entitlement to medical services, regardless of their financial situation (Bundesministerium für Gesundheit, 2022). The costs of care are covered and financed by the community of solidarity. “All insured persons share the costs incurred by the illness of individual members” (Bundesministerium für Gesundheit, 2022). The financial contribution of an insured person within the statutory health insurance is calculated individually based on their income (Bundesministerium für Gesundheit, 2022; SGB V, 2024). In the private health insurance system, the health insurance contribution is calculated on the basis of the insured person's “[...] state of health, age at entry and their individual health risk [...]” (Bundesministerium für Gesundheit, 2022). The solidarity-based community ensures that those with statutory health insurance do not have to pay for medical treatment in advance. All costs incurred are settled directly by the doctors and clinics with the health insurance funds after treatment (Bundesministerium für Gesundheit, 2022).

“Health insurance funds are self-governing legal entities under public law” (§ 4 SGB V, 2024). The health insurance funds organize and structure the provision of care. They determine “[...] how care is

organized and structured, and above all which medical treatments, operations, therapies, and medications are financed by health insurance funds and which are not [...]” (Bundesministerium für Gesundheit, 2022).

Statutory health insurance is the core of the German healthcare system and insures around 90% of the population (Bundesministerium für Gesundheit, 2024d). The services include health prevention measures, treatment and rehabilitation of the insured individuals (Bundesministerium für Gesundheit, 2024e). Health care is divided into primary care (outpatient treatment) and acute care (inpatient treatment). “The distinction and definitions of outpatient and inpatient services is traditionally derived from the place where the services are provided. Outpatient care services are defined as services provided outside of hospitals” (Nagel et al., 2017).

Outpatient Care

Outpatient treatment and services are provided by general practitioners, psychotherapists and specialists in non-medical health professions such as physiotherapists, occupational therapists and speech therapists. In Germany, it is necessary to be registered as a panel practitioner in order to be able to bill the statutory health insurance companies for the services provided (SGB V, 2024; Nagel et al., 2017).

The first contact with the healthcare system is usually with an outpatient medical service provider (Nagel et al., 2017). Access to health care in Germany is kept at a low level by the free choice of practitioner (Bundesministerium für Gesundheit, 2024b; SGB V, 2024).

Inpatient Care

Serious illnesses require a high level of medical or nursing care (Bundesministerium für Gesundheit, 2018). If the treatment goes beyond the scope of outpatient care, insured persons can be treated as inpatients in hospitals or specialist clinics such as preventive care and rehabilitation facilities (Bundesministerium für Gesundheit, 2024f). Due to the “the help of medical, nursing, functional, and medical-technical staff available at all times [...]” (§ 107 SGB V, 2024), hospitals are able to recognize “[...] patients' illnesses, prevent their worsening, [and] alleviate symptoms [...]” (§ 107 SGB V, 2024). They improve the state of health according to a medical treatment plan and promote the development of the patient's own defense and healing powers (§ 107 SGB V, 2024). The costs of accommodation and care are covered by health insurance, although those with statutory insurance must pay an additional contribution (Bundesministerium für Gesundheit, 2022).

Health Insurance Services

There is no standardized list of health insurance services (Bundesministerium für Gesundheit, 2024g). The German Social Security Code provides a framework of services that is adequate, appropriate and in line with the current state of medical science. The range of services extends from the right to services for the assessment of health risks and the early detection of diseases to the prevention of diseases and their progression and the treatment of diseases (§ 11 SGB V, 2024).

The focus of the services is on medical treatment, such as medical advice, services from the catalog of aids and remedies for physical or mental illnesses, and even surgical procedures (§§ 27, 33 SGB V, 2024). These include health check-ups, cancer screening, and behavior-related prevention courses on exercise, nutrition, and stress regulation (Bundesministerium für Gesundheit, 2024c). They also include vaccinations recommended by the Standing Committee on Vaccination for basic immunization (Ständige Impfkommision: Empfehlungen der Ständigen Impfkommision (STIKO) beim Robert Koch-Institut 2024). In addition, there is the option of home nursing and household help financed by the health insurance fund, as well as offers in the event of illness-related absence from work, in which the insured person is financially covered by sick pay (Bundesministerium für Gesundheit, 2024h).

Medication Coverage

Medications can be divided into prescription and non-prescription medications. Prescription medications in Germany are regulated by the Medicinal Products Act (AMG, 2024). Strongly effective medications or those associated with a particular risk of use and risk of efficacy are considered to be prescription-only. This ensures that therapy is only carried out after assessment by a physician and that it is under medical supervision (AMG, 2024; Bundesministerium für Gesundheit, 2024i). The majority of the costs are covered by the health insurance. For each prescription that is dispensed, the insured person has to pay ten percent of the sales price per pack, with a maximum cost limit of €10 (Bundesministerium für Gesundheit, 2024i).

Non-prescription medications, known as over-the-counter medications, are freely available in pharmacies and drugstores and are not subject to any direct or indirect risk to human health (AMG, 2024; SGB V, 2024). The selection is decided by the Gemeinsame Bundesausschuss (Bundesministerium für Gesundheit, 2024i). The costs of these medications are not reimbursed by the health insurance company and are not included in the insurance data (Bundesinstitut für Arzneimittel und Medizinprodukte, 2025; Bundesministerium für Gesundheit, 2024i; SGB V, 2024).

Palliative Care

At the end of life, health insurance covers a wide range of services for the insured. The costs of palliative and hospice care are not covered by the health insurance alone, but also by the social long-term care insurance (GKV-Spitzenverband, 2015). The health insurance fund also offers information on early options for personal provision for the end of life and helps with establishing contact with providers and claiming benefits (Bundesministerium für Gesundheit, 2024a; SGB V, 2024). The aim of outpatient palliative care is “[...] to enable the care of insured persons [...] in the familiar environment of their home or family” (§ 37b SGB V, 2024). Insured persons with advanced illness and severe symptoms that cannot be treated on an outpatient basis have the option of inpatient palliative care (§ 37b SGB V, 2024).

2.2. Care Outside the Healthcare System

Informal Care

Nonprofessional care (informal care) is a central component of the German care system outside the medical sector (DESTATIS, 2024b); mostly provided by family, friends or neighbors. Informal caregivers are individuals who provide unpaid, ongoing assistance to the person in need of care (Plöthner et al., 2019). This may include householding tasks such as shopping, cooking or cleaning, but also tasks of daily living such as washing, dressing or feeding (Goodhead & McDonald, 2007; Plöthner et al., 2019). The care is provided primarily by women, spouses or relatives of the person in need of care (Nowossadeck et al., 2016; Schmidt & Schneekloth, 2011; Wetzstein et al., 2015).

Social Networks

Social contacts create a framework for health-related behavior and health norms as well as for access to health promotion. They provide an exchange of information about resources and coping strategies, instrumental support through financial and emotional support (Seeman & Crimmins, 2001). Social support has been shown to have a positive effect on the health of those affected (Seeman, 1996; Valtorta et al., 2016). Social exchange and support reduce the risk of various illnesses such as depression or heart disease and can slow cognitive decline (Barnes et al., 2004; Valtorta et al., 2016). Physical and mental activation through visits to family and friends, social or religious institutions also had a positive effect on the activation of cognition and thus counteracted the process of decline (Fratiglioni et al., 2004). The number of different contact groups and the intensity of the contacts have

a lasting effect on health. The more contact groups available, the more resources a person can fall back on and benefit from the diverse range of support.

2.3. Health Care Situation in Germany

In Germany, care is provided by various actors: professional caregivers and caregiving relatives, with family members providing the majority of care (Brijoux & Zank, 2022; Kutzleben et al., 2017).

Around 86% of people in need of care in Germany are cared for at home, 55% of whom are cared for by relatives alone. Another 19% are cared for together with outpatient care services (DESTATIS, 2024b).

About 65% of informal caregivers are women and 35% are men (Wetzstein et al., 2015). Care is often provided by people with a low level of education, no employment and low social support (Wetzstein et al., 2015). Approximately 3 to 5 million relatives provide care in Germany (Nowossadeck et al., 2016; Schmidt & Schneekloth, 2011).

The percentage of women in need of care increases with age. From around 5.4% of women aged 60-69 in need of care, this figure rises to 91.4% for those aged 90 and older (DESTATIS, 2025a). This is due to the fact that women on average have a higher life expectancy than men (Dattani & Rodés-Guirao, 2023).

Studies on the current use of medications over the last seven days showed that 74.7% of adults used at least one medication (Knopf & Grams, 2013; Robert Koch-Institut, 2003). Considering the last 12 months, the number increased to around 91% of people who used medication (Robert Koch-Institut, 2003). Overall, the prevalence is higher among women than men. The highest prevalence was among 70- to 79-year-olds, with 94.9% of men and 96.3% of women taking medication (Knopf & Grams, 2013). The most frequently used medications were those for the treatment of the cardiovascular system (27.2% of men and 29.5% of women). Antibiotics for systemic use were rarely prescribed, with a prevalence of 1.7% overall; 1.2% for men and 2.1% for women (Knopf & Grams, 2013).

2.3.1. Health Care Situation of Dementia Patients in Germany

Approximately 70% of old dementia patients do not live in specialized care facilities, but rather in private homes (Brijoux & Zank, 2022). The majority of whom (39.4%) receive informal support from relatives (Brijoux & Zank, 2022). The utilization of outpatient care among dementia patients in a home care setting is low with 7.6%, with the use of day care being even less frequent at 2.9% (Brijoux & Zank, 2022). Most elderly dementia patients who do not live in private households live in nursing

homes (18.6%) or retirement homes, as well as alternative living arrangements such as multigenerational homes (5.6%), residential groups (1.3%), and senior residences (1.2%) (Brijoux & Zank, 2022).

Patients with dementia are admitted to hospitals and treated more frequently than patients without cognitive problems (Jacobs et al., 2017; Phelan et al., 2012). Dementia patients are more likely to have serious complications from minor illnesses, which is why they are admitted to the hospital more quickly than patients without dementia (Jacobs et al., 2017). This is also reflected in the growing number of inpatient hospital treatments for Alzheimer's patients; 82% more hospital treatments between 2001 and 2021 (DESTATIS, 2019, 2023a, 2023c).

The exact proportion of dementia patients in hospitals has been very uncertain until now because diagnoses are unknown, missing or not shared at the time of admission (Kirchen-Peters & Krupp, 2019). A diagnosis has already been documented for 37% of all patients with dementia (Scheel et al., 2020). The numbers vary between different studies between 18% - 40% (Kirchen-Peters & Krupp, 2019; Kurmann, 2023; Pinkert & Holle, 2012; Scheel et al., 2020). Exact numbers are difficult to obtain because dementia is rarely recorded as a diagnosis for a hospital stay. Patients with dementia are admitted to hospital for more serious secondary illnesses (Pinkert & Holle, 2012; Scheel et al., 2020; Stiefler et al., 2023). It is likely that in some cases the actual dementia prevalence has been underestimated. It is estimated that between 0.2% and 6% of patients are treated in hospital for dementia (Kurmann, 2023). "The probability or risk of hospitalization for persons with dementia is between 1.4–3.6 times greater than it is for non-dementia persons" (Pinkert & Holle, 2012).

Agents acting on the renin–angiotensin system (C09) and analgesics (N02) are among the most frequently prescribed medications for dementia patients in need of care (Storm, 2017). After a diagnosis of dementia, prescriptions for analgesics (N02) and antibiotics (J01) increase most notably compared to other medications (Storm, 2017). So far, there are only a few studies on antibiotic prescriptions in dementia patients. An analysis of all Allgemeine Ortskrankenkasse insured persons in 2020 showed that approximately 64% of dementia patients received long-term polypharmacy (five or more medications) (Schröder et al., 2022). The prevalence of antibiotic use varies between 3.3% and 16.6% depending on the study (van der Maaden et al., 2015). Studies conducted shortly before death revealed a higher prevalence of antibiotics for systemic use in dementia patients, ranging from 23.5% in the home environment (Hirakawa et al., 2006) to 73% in hospitals (Ahronheim et al., 1996). In a comparison between dementia patients and patients without dementia, dementia patients receive more antibiotic prescriptions at the time of diagnosis (72.93%) than non-dementia patients (69.85%) (Rakuša et al., 2023).

3. Theoretical Framework

This chapter describes the concept of health from the salutogenetic and pathogenetic perspective, the Andersen's behavioral model of health-related care utilization, and Jette and Verbrugge's disablement process, before embedding the individual studies in this framework. At the end of this chapter, old age and the end of life are explained.

3.1. Health

Health can be viewed from two different perspectives, the pathogenetic and the salutogenetic approach. The pathogenetic approach focuses on the development of disease and emphasizes the prevention of risk factors. Health is a state characterized by the absence of disease. Diagnosable symptoms and diseases are considered deviations from the normal state (Bhattacharya et al., 2020).

This contrasts with the salutogenesis approach coined by Aaron Antonovsky (Antonovsky, 1979). This approach does not define a dichotomy of health, but rather presents health and illness as a continuum. People's health status moves between two poles - health and illness - with actual health lying in between and varying according to life circumstances (Bhattacharya et al., 2020). The focus is on protective factors and health promotion that help maintain health along the continuum. Stressors and available resilience resources are seen as determinants of health (Bhattacharya et al., 2020; Faltermaier, 2023).

This thesis focuses on different approaches to the definition of cognition. Both the pathogenetic and the salutogenetic approaches were considered. Study I and Study II examine the pathogenetic health state of dementia, which was defined as a confirmed disease state and a deviation from the normal state based on medical diagnoses. Study III examines the progressive cognitive state on the continuum from no cognitive impairment to severe cognitive impairment. More detailed definitions are provided in Chapter 4.

3.2. The Andersen Model of Health Care Services Utilization (1995)

The behavioral model of health care service utilization developed by Andersen (Figure 1) is used to describe and explain the determinants of health care utilization (Andersen, 1995). The aim of the model is to analyze and understand the factors that influence the utilization of health-related services (Andersen, 1995). The focus is on predisposing factors, enabling factors and need.

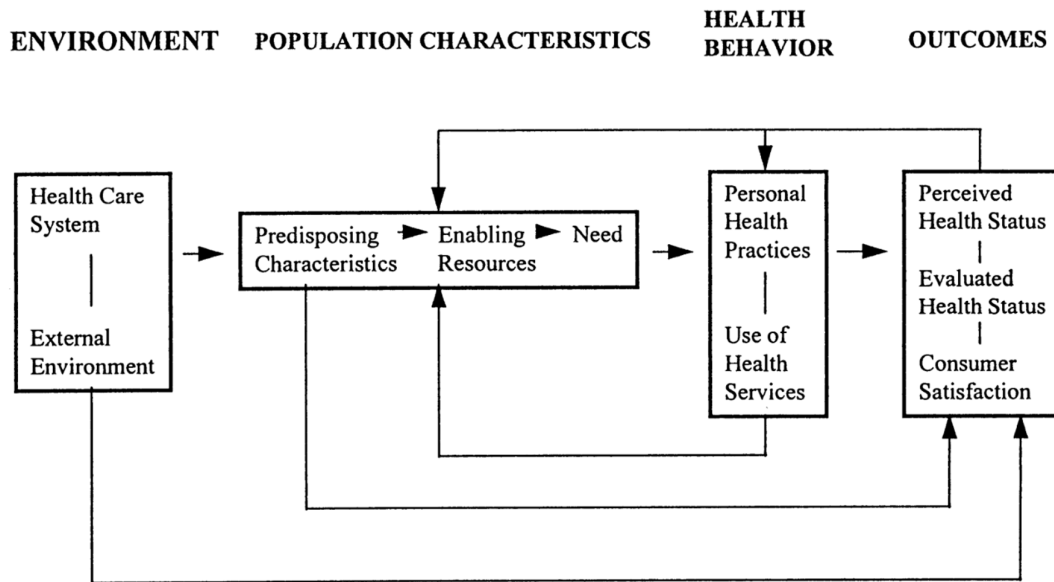


Figure 1. The Andersen model of health care services utilization (Andersen, 1995).

Predisposing factors determine the likelihood of use through biological characteristics. These include genes as well as demographic characteristics such as age and gender (Andersen, 1995; C. Chen & Gu, 2019). Individual health beliefs and knowledge of the healthcare system also contribute and influence the recognition of the need for health care services and, if necessary, their utilization behavior (Andersen, 1995; C. Chen & Gu, 2019).

The enabling factors encompass the social and material resources. These resources include personal, family, and community-related factors. They encompass access to social and health insurance, income, housing conditions, marital status, and the infrastructure of the residential environment, which ensures barrier-free access to care facilities (Andersen, 1995).

The need is divided into two categories: On the one hand, there is a subjectively perceived need, which relates to the presence and perception of symptoms. On the other hand, there is an objectively diagnosed need that has been determined externally, for example by a medical doctor (Andersen, 1995).

The population characteristics interact with actual health behavior. These include diet and nutrition, exercise, stress reduction, alcohol and tobacco consumption, self-care and compliance with medical regulations. The type, frequency and intensity of health care utilization vary depending on predisposing, enabling and needs-based factors (Andersen, 1995).

The results of the utilization of health care services are also divided into the subjectively and objectively perceived state of health and, on the other hand, satisfaction with care. This considers the accessibility and cost of care as well as the availability, financing and quality of care.

This model is embedded in the overall social context with health policy, organizational determinants and the environment. The provision of care options, social and health insurance as well as health policy decisions and strategies to increase public spending on health care represent political and economic aspects.

The results of political measures, changed environmental conditions and the so-called disposition characteristics have an impact on health outcomes. As a consequence, the outcome can modify health behavior in both positive and negative ways (Andersen, 1995).

3.3. Disablement Process

Within the domains of both pathogenetic and salutogenetic research, the state of health is influenced by a range of factors, including risk factors and protective factors. Interactions with society and the environment have been demonstrated to influence health and the effects of illness. The disablement process, as conceptualized by Verbrugge and Jette (Verbrugge & Jette, 1994), delineates the progression from a healthy state to the development of pathology, physical and cognitive impairment, functional limitation, disability, and limitations in everyday life. The disablement process is influenced by a multitude of risk and protective factors, and environmental elements (Verbrugge & Jette, 1994). These factors exert influence at various points in the process and can be targeted through specific measures.

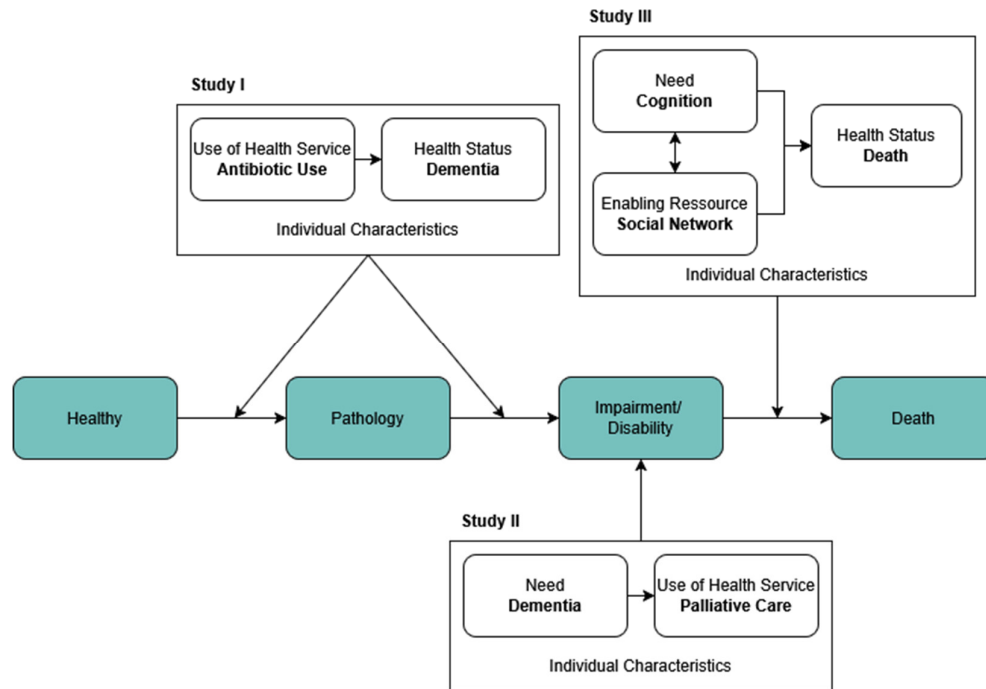


Figure 2. Adaption of disablement process and health care services utilization model (Andersen, 1995; Verbrugge & Jette, 1994).

Figure 2 shows an adaptation of the disablement process and health care services utilization model (Andersen, 1995; Verbrugge & Jette, 1994). From a healthy cognitive state, through the development of pathology, disability and functional limitation, to death. The individual studies in this work examine various risk and protective factors at different points in this process.

3.4. Old Age

Neugarten and Laslett introduced the terms “Third Age” and “Fourth Age” to describe older age groups, including the young old and the old-old individuals (Laslett, 1991; Neugarten, 1974). These age groups have no fixed age limits and are therefore fluid. The “Third Age” is the period of life following retirement, characterized by an active, self-determined lifestyle in a physically and mentally healthy state (Neugarten, 1974; Wahl & Ehni, 2020). This period of life typically occurs between the ages of 60 and 80 years (Wahl & Ehni, 2020). The “Fourth Age” follows the “Third Age” and is characterized by loss of social contacts, restricted lifestyles, and frailty (Neugarten, 1974; Wahl & Ehni, 2020).

“Biological aging is defined as the natural occurrence of irreversible, increasing with age changes in metabolism and the physicochemical properties of cells [...]” (Dziechciaż & Filip, 2014), which can lead

to impairment and death. Older individuals are often characterized by multiple age-related comorbidities, such as hearing loss, diabetes, cognitive decline, and frailty, which often manifest concurrently (World Health Organization, 2024). In the existing literature on population and aging, old age is commonly defined between 60 and 65 years of age (DESTATIS, 2025c; United Nations et al., 2019; World Health Organization, 2024). Studies I and III of this thesis define old age according to the World Health Organization (WHO), which defines it as beginning at 60 years of age (World Health Organization, 2024).

3.5. End of Life

The end of life refers to the period before death, that is characterized by frailty and the near end of life (Lamont, 2005; Wahl & Ehni, 2020). This period is characterized by the progression of one or more diseases, frailty, and functional limitations until death (Koller & Rockwood, 2013; Lamont, 2005; Morgan et al., 2019). According to the literature, this period can last from a few days to several years before death (J.-H. Chen et al., 2007; Cohen-Mansfield et al., 2018) and is independent of biological age. In Study II of this thesis, end of life is defined as the final twelve months of an individual's life.

4. Cognition and Dementia

As the population ages, cognitive impairment has become a serious health and social challenge, associated with financial costs, personal burdens, and societal consequences (Deary et al., 2009). Cognition and dementia are the focus of this thesis and are introduced and defined in this chapter.

4.1. Cognitive Decline in Aging

The decline in cognitive ability is associated with the process of normal aging and is due to various degenerative processes (López-Otín et al., 2013). The loss of cognitive function is manifested in executive functions, processing speed and logical thinking (Bhattarai & Nagaraj, 2023; Deary et al., 2009). This can disrupt the process of accessing information from both long-term and short-term memory (Bhattarai & Nagaraj, 2023). However, despite this limitation, people with age-related cognitive decline can largely manage their daily lives and everyday tasks independently.

4.2. Cognitive Impairment

Cognitive impairment is defined as a measurable yet non-severe deterioration in cognitive abilities that extends beyond the normal aging process and a person's level of education (Gauthier et al., 2006; Winblad et al., 2004). Individuals with cognitive impairment encounter challenges with memory, language, thinking, and judgment, yet these do not substantially impact their daily activities (Gauthier et al., 2006). Cognitive impairment can be an early stage of Alzheimer's disease or other dementias, although dementia does not necessarily develop (Winblad et al., 2004).

Definition of Cognitive Impairment in Study III

In Study III, cognitive function was assessed using the neuropsychological test batteries Semantic Fluency Task, two Immediate Recalls of a 12-Word List, two Stroop Color-Word Tasks and a Delayed Free Recall of the 12-Word List. The test batteries measured cognitive functions of episodic memory, working memory and processing speed (Kleineidam et al., 2023). An overview is provided in Table 1. The analyses included a salutogenetic approach to cognitive status on the continuum between no impairment and severe impairment (graded to: low, moderate and high).

Table 1. Description of the cognitive test battery used for study III (Kleineidam et al., 2023).

Test	Description	Cognitive function
Semantic Fluency Task	As many different animal names as possible must be named within 60 seconds.	Processing speed, semantic memory
Immediate Recall of a 12-Word List	A list of twelve words is presented three times in a row and must be memorized for immediate recall. After each round, as many of the words as possible must be repeated. Ten of the twelve words correspond to the CERAD-Plus neuropsychological test battery word list.	Episodic memory
Stroop Color Tasks	The names of 36 colors written in color must be read correctly. The ink color is incongruent to the written word and the ink colors must be named correctly. The time required to complete this task is measured.	Processing speed
Delayed Free Recall of the 12-Word List	As many words as possible must be recalled from the "Immediate Recall of a 12-Word List" test within 60 seconds without being presented again (delayed recall).	Episodic memory

4.3. Dementia

Dementia is not part of natural aging. The disease is a complex of different causes, symptoms, manifestations and progressions (World Health Organization, 2017). The International Classification of Disease and Related Health Problems (ICD-10) defines dementia as follows:

“Dementia (F00-F03) is a syndrome characterized by impairment of higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning aptitude, language and judgment. Consciousness is not impaired. Cognitive impairment is usually accompanied by changes in emotional control, social behavior or motivation, but occasionally these occur earlier. This syndrome occurs in Alzheimer's disease, cerebrovascular disorders and other conditions that primarily or secondarily affect the brain.” (Weltgesundheitsorganisation, 2006)

A distinction can be made between primary and secondary dementias based on the underlying causes (Stoppe & Staedt, 2002; Wiltfang et al., 2017). Around 90% of dementias are primary dementias, which are irreversible and involve organic brain damage (Wiltfang et al., 2017). Primary dementias include neurodegenerative forms such as Alzheimer's dementia, Lewy body dementia and frontotemporal dementia. They also include non-neurodegenerative forms such as vascular dementia, infection-related dementia and hereditary forms. Approximately 10% of all dementias are secondary dementias and are mostly reversible, non-organic brain damage (Wiltfang et al., 2017). These include dementias caused by deficiencies such as infections, intoxication from alcohol and drugs, head injuries and metabolic diseases.

Alzheimer's dementia is the most common form of dementia (50% - 70%) followed by vascular dementia (15%) (Alzheimer's Disease International, 2023; Wiltfang et al., 2017; World Health Organization, 2017). Rare forms of dementia, including frontotemporal dementia, Lewy body dementia, and dementia caused by Parkinson's disease, account for approximately 10% of all dementia cases (Georges et al., 2023; Winblad et al., 2016). Most dementia patients have a mixed form at the end of their lives (Rabinovici et al., 2017).

Definition of Cognitive Impairment in Study I and Study II

Study I and Study II classified dementia using the International Classification of Diseases, 10th Revision (ICD-10) (World Health Organization, 2004). The majority of the dementia diagnoses were classified as unspecified dementia (Fink, 2014). For this reason, no distinction was made between the subtypes of

dementia in the present studies and the following ICD-10 codes were assigned to all-cause dementia: F00/G30 Alzheimer's disease/dementia, F01 Vascular dementia, F02 Dementia with disease elsewhere classified, F03 Dementia not otherwise specified, F051 Delirium with dementia, G310 frontotemporal dementia and G3182 Lewy body dementia (World Health Organization, 2004). The classification was implemented as binary coding (dementia diagnosis vs no dementia diagnosis).

4.4. Epidemiology of Cognitive Impairment and Dementia

In 2019, dementia affected more than 48 million people over the age of 65 worldwide, and this number is estimated to continue increasing (World Health Organization, 2021) (Figure 3). Forecasts indicated that by the year 2050, the number of individuals aged 40 and over affected by dementia will reach 139 million (World Health Organization, 2021). In Europe, the number of individuals aged 65 and older living with dementia is estimated to rise from 7.9 million in 2021 to 15.9 million by 2050 (Alzheimer Europe, 2020; Deutsche Alzheimer Gesellschaft e. V.; Eurostat, 2025).

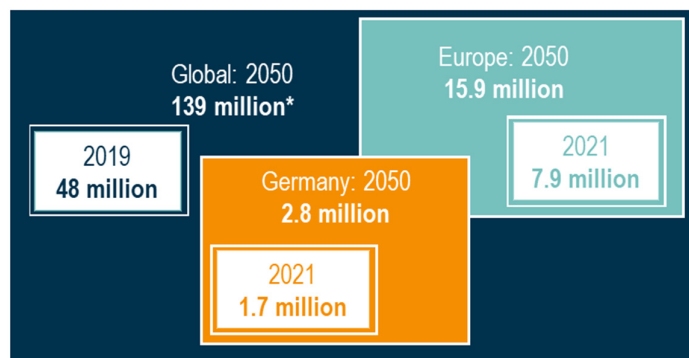


Figure 3. Number of people with dementia (million) for the years 2021 (Global 2019) and 2050 from the age of 65. *From age 40 (Alzheimer Europe, 2020; Deutsche Alzheimer Gesellschaft e. V.; Eurostat, 2025; World Health Organization, 2021).

In 2021, approximately 1.8 million individuals across Germany were affected by dementia, 1.7 million of whom were over the age of 65 (Deutsche Alzheimer Gesellschaft e. V.), and forecasts also pointed to a future increase in the number of people affected. By 2050, the number of individuals aged 65 and over could reach up to 2.8 million (Deutsche Alzheimer Gesellschaft e. V.).

With increasing age, the number of dementia patients rises exponentially. Up to the age of 80 to 84, the number of dementia patients doubles approximately every five years (Georges et al., 2023). From age 85 onward, the prevalence growth slows down, and individuals over 90 years have the highest prevalence (Georges et al., 2023). Notably, women constitute approximately two-thirds of all affected individuals, a phenomenon attributable to biological differences between the sexes, augmented life expectancy among women, and differential exposure to risk factors (Andrew & Tierney, 2018; Dattani & Rodés-Guirao, 2023).

Mortality

People with dementia have a higher mortality than people without dementia, with the average survival of people with dementia being 3 - 9 years after initial diagnosis at age 65 or older (Deutsche Alzheimer Gesellschaft e. V.; Winblad et al., 2016). Age at diagnosis, gender, and the etiology of dementia influence the life expectancy of dementia patients (Brodaty et al., 2012; Liang et al., 2021). Women have a higher life expectancy than men, so they are more likely to live longer with dementia and to remain in the severe stage for longer (Dattani & Rodés-Guirao, 2023; Winblad et al., 2016). Currently, dementia mortality can only be assessed with limitations based on cause-of-death statistics, which primarily report the underlying condition that led to death. However, dementias are more likely to be considered as a contributory cause of death and are therefore much less frequently recorded in cause-of-death statistics (Küppers et al., 2021; Winblad et al., 2016).

Doblhammer et al. reported that between 2014 and 2017, dementia was the most common comorbidity at the time of death in women aged 70 years and older and the fifth most common comorbidity in men (Doblhammer et al., 2022). Forecasts indicate that, by 2060, dementia may become one of the leading comorbidities at the time of death for both women and men.

5. Risk Factors of Cognitive Impairment and Dementia

In the following section, the most relevant risk factors for this work are presented in detail. The risk factors were assigned to predisposing characteristics, enabling resources and need factors.

5.1. Predisposing Characteristics

Genetics and Microbiomes

The most important genetic risk factor in late onset Alzheimer's dementia is Apolipoprotein E (ApoE) (Kim et al., 2009). The protein fulfills the role of a nutrient supplier for brain cells and comes across in the variants ApoE2, ApoE3, and ApoE4. ApoE4 has been shown to disrupt the supply of nutrients to brain cells and accelerate the clumping of amyloid in the brain. This, in turn, disrupts signal transmission between nerve cells and causes their death (Braak & Braak, 1995; Kim et al., 2009; Parhizkar et al., 2019). Tau protein has also been linked to Alzheimer's disease. In this case, the tau protein no longer functions properly, leading to the formation of tau fibrils. This, in turn, results in the loss of function and death of the nerve cells (Braak & Braak, 1995; Mandelkow & Mandelkow, 1998).

The gut microbiome has been shown to support health by producing neurotransmitters and regulating nerve signaling (Łuc et al., 2021). Metabolic changes in the gut microbiome have been shown to lead to the formation of intestinal toxins and inflammatory reactions (Bauer et al., 2016; Łuc et al., 2021). Dysbiosis, a condition marked by an imbalance in the composition of the gut microbiome, has been associated with altered protein expression, amyloid deposits, and regional inflammatory reactions. The disruption of signaling protein synthesis and subsequent disturbance of metabolic and inflammatory pathways have been linked to neuronal damage (Angelucci et al., 2019; Łuc et al., 2021; K. Meyer et al., 2022). This neuronal damage is associated with cognitive decline and various neurological and neurodegenerative diseases, including Alzheimer's disease (Łuc et al., 2021; K. Meyer et al., 2022).

Age

Age is the greatest risk factor for dementia (Alzheimer's Association, 2025). The development of dementia begins gradually and symptoms only manifest themselves over time. Due to the gradual process of the disease, clinically visible symptoms usually appear late and the disease has already caused severe irreversible brain damage (Alzheimer's Society, 2021). With increasing age, there are

also other diseases of old age that promote cognitive decline. These include high blood pressure, stroke, a weaker immune system and an increased risk of infections, as well as a decrease in cell activity in the brain (Alzheimer's Society, 2021; Alzheimer's Association, 2025).

Sex

Up to the age of 80, men and women have a similar risk of dementia (Alzheimer's Society, 2021). Women are more likely to develop Alzheimer's dementia, while men are more likely to develop vascular dementia (Doblhammer et al., 2012; McCullagh et al., 2001). Gender differences result from biological differences between men and women (Andrew & Tierney, 2018), differences in life expectancy (Alzheimer's Society, 2021; Dattani & Rodés-Guirao, 2023), different exposure to risk factors (Andrew & Tierney, 2018), education and the opportunity for lifelong mental stimulation (Alzheimer's Society, 2021).

Education

Individuals with a low level of education have a higher risk of dementia than individuals with a higher level of education (McCullagh et al., 2001). This correlation can be attributed, at least in part, to the healthier lifestyle that people with a higher level of education tend to adopt. Education confers a multitude of benefits, including social, psychosocial, and economic advantages, thereby promoting socioeconomic development, enhancing empowerment, and fostering social mobility. Consequently, education contributes to health and survival (Baker et al., 2017; Balaj, 2024; Park & Kang, 2008). Individuals with a higher level of education possess a greater cognitive reserve capacity, which enables them to compensate for cognitive decline (Livingston et al., 2020; McCullagh et al., 2001; Meng & D'Arcy, 2012).

5.2. Enabling Factors

Income

In order to utilize health care services, it is necessary to have both community and personal resources available (Andersen, 1995). In Germany, the fundamental prerequisite for accessing health care services is health insurance, which covers a portion or the entirety of health care expenditures (Bundesministerium für Gesundheit, 2022, 2024e; SGB V, 2024). In cases where costs are not fully covered by health insurance, income also plays an important role in the ability to use or afford

individual health care services (Ärztliches Zentrum für Qualität in der Medizin [ÄZQ], 2012; SGB V, 2024).

Social Contacts

The influence of an absence of social networks on mortality is comparable to other known risk factors, such as smoking and alcohol consumption (Holt-Lunstad et al., 2010; Laugesen et al., 2018). Furthermore, an association has been identified between an elevated level of social integration and a lower risk of cognitive impairment and dementia in older people (Barnes et al., 2004; Ellwardt et al., 2015; Fratiglioni et al., 2004). Social support and social interaction have been demonstrated to facilitate coping with intellectual challenges in late adulthood (Schooler & Mulatu, 2001) and protect against cognitive decline (Bosma et al., 2003).

5.3. Need Factors

Infections

A close link has been demonstrated between pathological changes in the brain and immune responses in both infectious delirium and Alzheimer's disease (van Peters Ton et al., 2020). There is strong evidence that most neurodegenerative diseases are triggered by systemic inflammation caused by peripheral infections such as bacterial sepsis, periodontitis, but also autoimmune diseases, all of which can initiate activation of local immune responses in the brain (Balducci & Forloni, 2019; Iwashyna et al., 2010; Kamer et al., 2008; Manabe & Heneka, 2022; Perry, 2004; Weaver et al., 2002; Whitson et al., 2022; Yaffe et al., 2003). Infection-related inflammatory episodes, particularly in elderly individuals, have been demonstrated to exacerbate the processes within the brain that underlie cognitive decline. This suggests a potential for infections to accelerate cognitive decline in individuals with and without clinical symptoms (Perry, 2004).

Diabetes

Diabetes mellitus (type 2) and prediabetes have been identified as risk factors for all-cause dementia (Buchmann et al., 2019; Cheng et al., 2012; Haroon et al., 2015; Reinke et al., 2022; Xue et al., 2019). The duration and severity of the disease have been demonstrated to promote cognitive impairment (Roberts et al., 2008). Chronically high blood glucose levels cause damage to blood vessels in the brain, which increases the risk of oxidative stress, inflammation, and microvascular changes (Haroon et al.,

2015; Strachan et al., 2011). This, in turn, results in a decline in cognitive performance. Conversely, low blood glucose levels have also been demonstrated to cause brain damage by increasing the risk of vascular damage to the brain (Exalto et al., 2012; Haroon et al., 2015; Whitmer et al., 2009), and damaging learning and memory regions (Whitmer et al., 2009).

Hypertension

Hypertension has been demonstrated to induce circulatory disturbances within the brain, thereby heightening the risk of cerebrovascular disease, impairment to the blood-brain barrier, vascular dementia, and Alzheimer's disease (Canavan & O'Donnell, 2022; La Torre, 2012; McCullagh et al., 2001; Ou et al., 2020). In particular, in the middle-aged population, high blood pressure is regarded as a substantial risk factor for the onset of dementia (Canavan & O'Donnell, 2022; Hughes et al., 2020; McCullagh et al., 2001; Schaare et al., 2019). Recent meta-analyses investigating the relationship between antihypertensive medication and the influence of treated hypertension on the risk of dementia have indicated a reduced risk of cognitive impairment and dementia due to antihypertensive medication (Hughes et al., 2020; Ou et al., 2020).

Heart Disease

Cardiovascular disease has become an important risk factor for the development of cognitive decline and Alzheimer's disease (Livingston et al., 2020) and manifests itself together in many cases (Doblhammer et al., 2012). In particular, the joint occurrence of various cardiovascular diseases increases the risk of cognitive decline (Lamar et al., 2022). In coronary heart disease, plaques accumulate on the vessel walls (La Torre, 2012). These are not only limited to heart disease vessels, but also lead to deposits in blood vessels of the brain, which promotes the development of dementia (Gorelick et al., 2011). If a plaque accumulation suddenly dissolves, this can cause thrombosis and lead to vasoconstriction, which can trigger a heart attack or stroke (La Torre, 2012).

Lifestyle Factors

Smoking increases the risk of dementia (Livingston et al., 2020; J. S. Meyer et al., 1999; Raggi et al., 2022; Zhong et al., 2015). The consumption of cigarettes can trigger oxidative stress and inflammatory processes and thus lead to neuronal damage (Wang et al., 2025). Cerebrovascular structures are also destroyed, preventing adequate blood supply to the brain and leading to long-term cognitive decline and Alzheimer's disease (Wang et al., 2025).

Similar to smoking, consuming alcohol more than half of the week, up to daily consumption, triggers oxidative stress and inflammation. This can lead to neuronal damage and an increased risk of cognitive impairment and dementia (Livingston et al., 2020; Wang et al., 2025). In addition, regular excessive alcohol consumption attacks the neurotransmitter system and strongly promotes cognitive decline and the development of dementia (Wang et al., 2025).

In addition to the factors mentioned, a number of other variables were included in the studies of this thesis. Table 2 provides a detailed overview of all included predisposing characteristics, enabling factors and need factors.

Table 2. Overview of all included predisposing characteristics, enabling factors and need factors that were included in the studies of this thesis.

	Predisposing Characteristics	Enabling factors	Need factors
Study I	age, sex		gastrointestinal infections, pneumonia, respiratory infection, bladder and urinary tract infections, skin infections, sepsis, bacterial meningitis, meningococcal infection, and lyme disease, congestive heart failure, cardiac arrhythmias, valvular disease, pulmonary circulation disorders, peripheral vascular disorders, hypertension, paralysis, other neurological disorders, chronic pulmonary disease, diabetes, hypothyroidism, liver disease, peptic ulcer disease (excluding bleeding), AIDS/HIV, lymphoma, metastatic cancer, solid tumor without metastasis, rheumatoid arthritis/collagen vascular diseases, coagulopathy, obesity, weight loss, fluid and electrolyte disorders, blood loss anaemia, deficiency anaemia, alcohol abuse, drug abuse, psychoses, depression, long-term care, nursing home residency, hospitalization
Study II	age, sex		cancer diagnosis, dementia diagnosis, physiotherapy, occupational therapy, speech therapy, other therapies (excluding physiotherapy, occupational therapy, and speech therapy), rehabilitation, chemotherapy, nuclear therapy, radiotherapy, cancer drugs, dementia drugs, congestive heart failure, cardiac arrhythmias, valvular disease, pulmonary circulation disorders, peripheral vascular disorders, hypertension, paralysis, other neurological disorders, chronic pulmonary disease, diabetes, hypothyroidism, liver disease, peptic ulcer disease (excluding bleeding), AIDS/HIV, rheumatoid arthritis/collagen vascular diseases, coagulopathy, obesity, weight loss, fluid and electrolyte disorders, blood loss anaemia, deficiency anaemia, alcohol abuse, drug abuse, psychoses, depression
Study III	age, sex, marital status, mother tongue	social contacts, place of investigation, income, education, employment status	cognition, stroke, myocardial infarction, systolic heart failure, peripheral arterial disease, diabetes mellitus, tumor disease, leukemia and AIDS, BMI

6. Materials and Methods

The chapter presents data from the Allgemeine Ortskrankenkasse and the German National Cohort, as well as the methods used in the studies of this thesis.

6.1. Data Sources

6.1.1 Data of the Allgemeine Ortskrankenkasse

The Allgemeine Ortskrankenkasse (AOK) is Germany's largest statutory health insurance fund, which insures about one-third of the German population. More than 44% of people in need of care in Germany are insured with the AOK (Schwinger et al., 2024; DESTATIS, 2025a).

The AOK data are nationwide, anonymized health claims data of AOK insured persons, which consist of data from the inpatient and outpatient sectors. This data is collected by the Scientific Institute of the AOK (WIdO). The data set encompasses demographic information, including sex, month of birth and death (if applicable), place of residence, and institutionalization status. Additionally, the sample encompasses all inpatient and outpatient diagnoses, coded according to ICD-10 (World Health Organization, 2004). The data set also includes filled prescriptions for medications, which are coded according to the Anatomical Therapeutic Chemical Classification of Drugs and Medicines (ATC) (Bundesinstitut für Arzneimittel und Medizinprodukte, 2025). The WIdO collects this data from insured persons on a quarterly basis, and it is available at the individual level on a quarterly basis.

“Health claims data from health insurance companies are now well established as a data source in health services research, epidemiology, and medical sociology” (Epping et al., 2021). Unfortunately, German health insurance data are not representative of the general German population. The socio-demographic and socio-economic distribution of the population varies between the health insurance funds and in relation to the general population (Hoffmann & Icks, 2012). AOK policyholders exhibit a higher proportion of older individuals, a lower educational level, and a lower income compared to the general population (Epping et al., 2021). Due to the free choice of health insurance provider, sudden drop-outs due to switching can occur in the data.

Data samples of study I and study II

Two different samples, each with a size of 250,000 individuals, were used for the analyses in Study I and Study II. AOK Data sample A (Study I) included individuals aged 50 and over during the period from 2004 to 2019. AOK data sample B (Study II) comprised individuals aged 50 and older from 2014 to 2019.

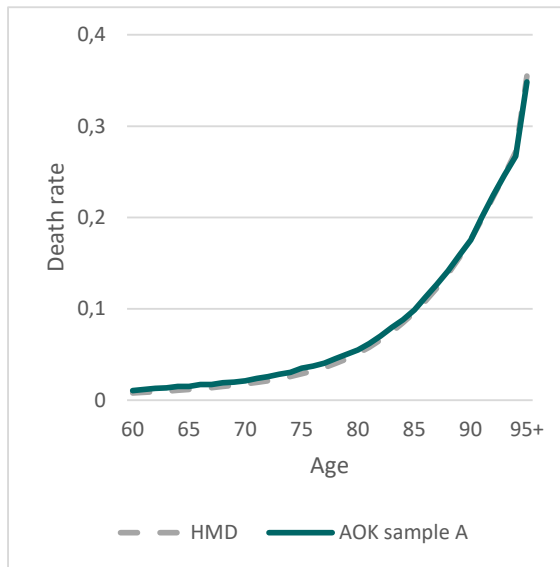


Figure 4. Death rates (2006-2018) for the AOK sample A and Germany (Human mortality database (HMD, 2025)).

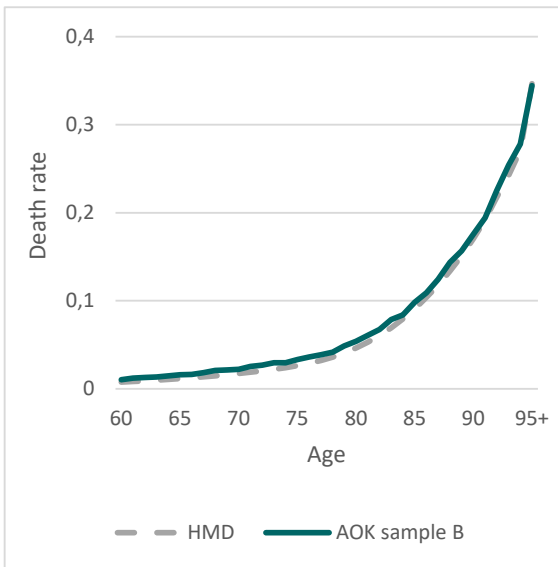


Figure 5. Death rates (2014-2019) for the AOK sample B and Germany (Human mortality database (HMD, 2025)).

Fink et al. already showed that the AOK sample was representative of the German population aged 65 and over in terms of mortality (Fink, 2014, 2017). The updated representations of the results for the individual AOK samples used in the studies in this thesis are shown in Figure 4 and Figure 5 for the respective observation period of the study. Both data samples are representative of the German population in terms of mortality from the age of 60.

Similarly, the prescription of inpatient palliative care at the end of life within the AOK sample B is comparable to other German health insurance funds (Figure 6). The number of prescriptions for outpatient palliative care from 2018 onwards was slightly higher for AOK members than for members of other health insurance funds.

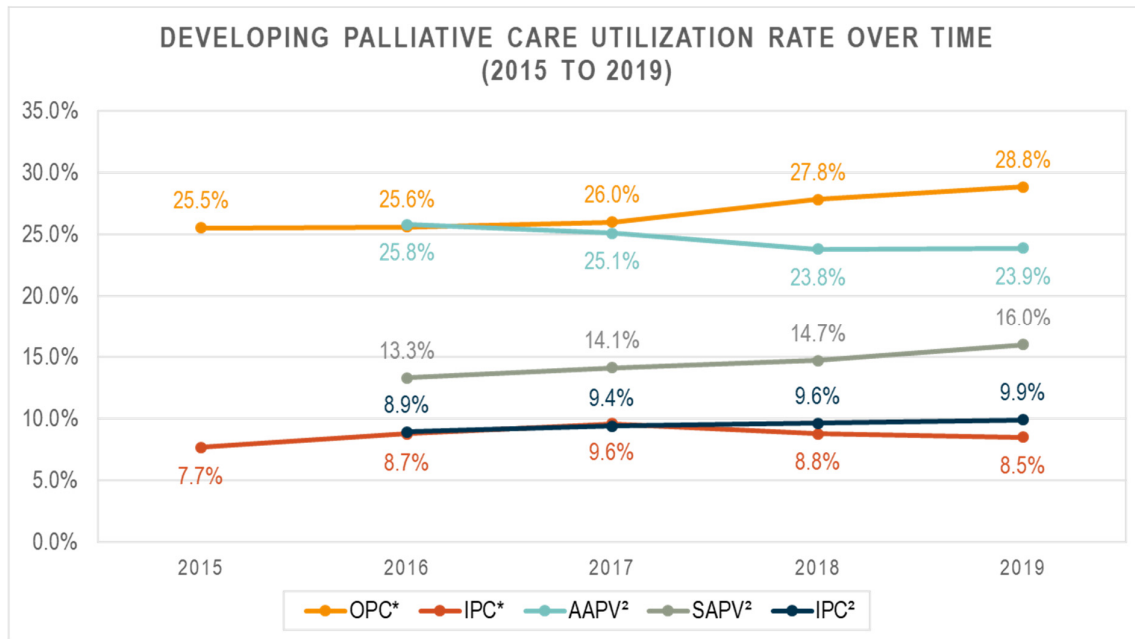


Figure 6. Developing palliative care utilization rate over time (2015 to 2019) (Rakuša et al., 2025).
OPC: Outpatient palliative care; IPC: Inpatient palliative care; * Utilization rates from AOK Data sample B; ²Utilization rates of BARMER-insured persons from Ditscheid et al. (Ditscheid et al., 2023).

To avoid the problem of false-positive dementia diagnoses, an established internal two-stage validation strategy were used (Doblhammer et al., 2015; Taylor et al., 2009). First, only physician-verified outpatient diagnoses as well as inpatient discharge and secondary diagnoses were used. Next, diagnoses were considered valid if they were confirmed by simultaneous inpatient and outpatient diagnoses, as well as two diagnoses from two different doctors within the same quarter. If a person died within the same quarter that dementia was first diagnosed, the diagnosis continued to be considered valid.

6.1.2. German National Cohort (NAKO)

The German National Cohort (NAKO), a large-scale prospective epidemiological study, is designed to investigate health and disease in Germany (German National Cohort (NAKO) Consortium, 2015). The aim is to create a research platform for future epidemiological population-based research in order to achieve the following:

1. “Identification of etiological pathways from life-style and environmental risk factors to major chronic diseases and functional impairments” (German National Cohort (NAKO) Consortium, 2015).
2. “Studies of the geographic and socio-economic disparities in health status and disease risks in Germany and possible causes and explanations” (German National Cohort (NAKO) Consortium, 2015).
3. “Development of risk prediction models for identifying individuals at increased risk of developing major chronic diseases, so as to allow personalized prevention strategies” (German National Cohort (NAKO) Consortium, 2015).
4. “Evaluation of markers for early detection of disease and pre-disease phenotypes, so as to develop effective tools for disease prevention” (German National Cohort (NAKO) Consortium, 2015).

Between 2014 and 2019, about 200,000 individuals aged 20 to 69 were recruited through a nationwide network of 18 study centers. All study participants were randomly selected based on age- and gender-specific samples from the population registers of the study areas and cover populations from metropolitan, urban and rural areas (German National Cohort (NAKO) Consortium, 2015; Peters et al., 2022). Questionnaires, clinical examinations and biomarker analyses provided information on the participants' genetic characteristics, demographics, health conditions, lifestyle factors, environmental exposures and social networks at baseline (German National Cohort (NAKO) Consortium, 2015; Peters et al., 2022). In addition, sub-cohorts were selected and invited for further measurements and surveys. The level 2 cohort, a 20% representative sample (40,000 individuals) of the total cohort, received an extended examination program on general health and extended cognitive function tests (German National Cohort (NAKO) Consortium, 2015). Whole-body MRI was performed in 40,000 randomly selected individuals to identify morphological and functional changes over time (German National Cohort (NAKO) Consortium, 2015). This cohort was selected from the basic cohort and may include individuals who were also selected for level 2 examinations. All examinations, questionnaires and interview contents of the cohorts are listed in Table 3.

Table 3. Overview of the examinations, questionnaires and interview content of the various cohorts (German National Cohort (NAKO) Consortium, 2015; Peters et al., 2022; Schipf et al., 2020).

	Baseline examination	Level 2 Cohort	MRI Cohort
Interviews	nationality, ethnicity, native language, family status, housing situation, education, employment/profession/status, income, partners and parent's education, occupation, diseases and syndromes, operations, questions of mini international neuropsychiatric interview vs 5.0, part major depression, medication use (past 7 days). Only women: menstrual cycle, contraceptives, menopause, hormone replacement, polycystic ovary syndrome, HPV	Complete mini questionnaire module on major depression,	
Questionnaires	Health-related quality of life, family history, childhood/youth, occupation, social networks and support, tattoos and solarium, physical activity and fitness, Smoking, alcohol consumption, drug use, family planning, infections, medical behavior, medical history, diet	Pain mannequin, seeing and hearing, restless legs syndrome, exposure to animals, work-related exposures/occupational stress	
Physical medical examinations	Anthropometric measurements, body composition and bone mineral density using dual-energy X-ray absorptiometry, blood pressure measurements, aortic pulse wave velocity measurement, electrocardiogram, 3D echocardiography, spirometry, physical activity measurements, physical fitness test, cognitive tests and tooth counting	Oral glucose tolerance test, carotid ultrasonography with measurement of intima-media thickness, 24-hour ECG, sleep apnea assessment, extended motor, sensory and cognitive testing, FeNO test, dental examination	Whole-body MRI
Biological samples	Blood, urine, saliva, nasal and stool tests		

Follow-up surveys are planned for all participants at five-year intervals after completion of the baseline survey (Figure 7). During these follow-up visits, the participants will receive the same examination program as during the baseline survey, and the extended level cohorts will again receive all additional level-specific questionnaires and examinations. In addition, every two to three years all participants will receive a short questionnaire on their current lifestyle and health status (German National Cohort (NAKO) Consortium, 2015; Peters et al., 2022). As the study progresses and further data are collected, the NAKO will provide a comprehensive database for future studies, including not only epidemiological information but also sociodemographic and lifestyle factors. The planned linkage with data from the statutory and private health insurance funds, the German Federal Pension Insurance, individual pension insurance providers, data from the Institute for Employment Research, the epidemiological cancer registry and the clinical cancer registry offers a unique interdisciplinary database to promote the understanding and prevention of diseases.

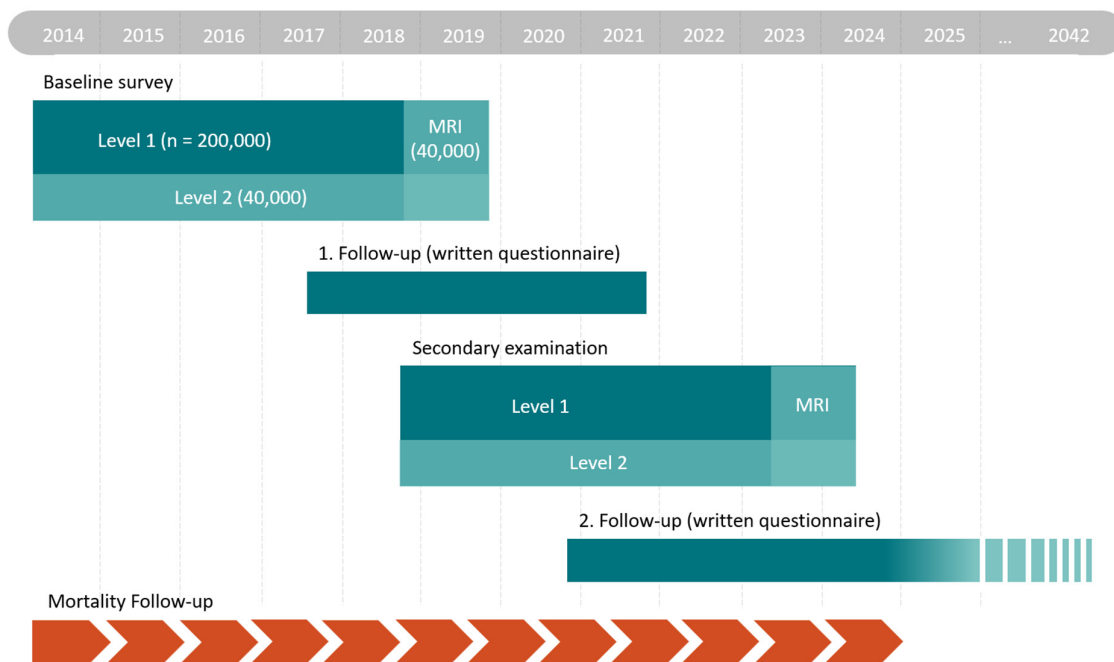


Figure 7. Overview of the NAKO data structure. Adapted from (German National Cohort (NAKO) Consortium, 2015; Schipf et al., 2020).

Mortality Follow-up

The NAKO mortality follow-up determines the date, place, type and cause of death for all deaths (Mueller et al., 2015). The deaths were coded according to the ICD-10 (World Health Organization, 2004). To record the deaths, the Competence Center for Mortality Follow-Up conducted regular, case-related surveys of the vital data of the study participants. Data collection was carried out through active follow-up, in which participants received written follow-up questionnaires on their health at two- to three-year intervals. In addition, the treating physicians and hospitals were contacted. Passive follow-up was carried out on the basis of secondary data (Kuss et al., 2022). The cause(s) of death for deceased persons were linked to the NAKO data via the information on the death certificate and other clinical and other documentation (Federal Institute for Population Research, 2024).

Data sample of study III

For the analyses of Study III, a subsample from the NAKO data was used with individuals aged 60 and

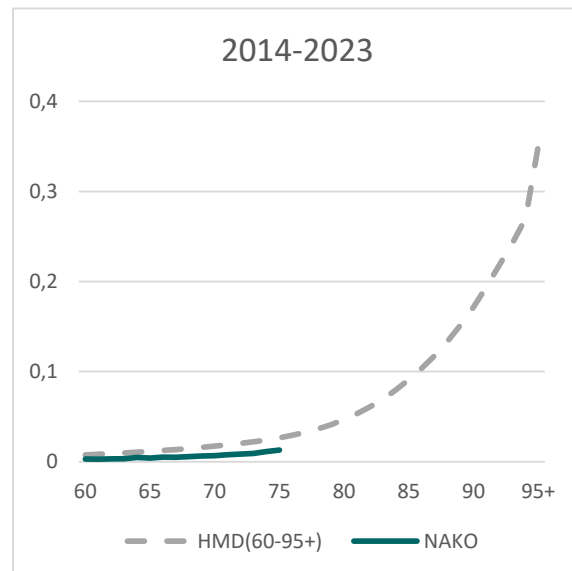


Figure 8. Death rates (2014-2023) for the NAKO sample and Germany (human mortality database (HMD, 2025)).

older. The individuals were observed from the time of the baseline survey until the end of December 2023. The sample is representative of the German general population in terms of gender distribution (Table 4). In terms of age distribution, it has a higher proportion of middle-aged people compared to the general German population. In addition, the NAKO participants have a comparatively higher level of education; with over 90% of people having completed upper secondary and higher education, compared to around 57% in the German population. In terms of mortality, the sample was not representative of the German population aged 60 and older (Figure 8). The death rates in the NAKO were lower.

Table 4. Gender and Age distribution of NAKO data and Mikrozensus data.

	NAKO	Mikrozensus
Sex		
Male	49.54	49.34
Female	50.46	50.67
Age		
<20	0.004	18.40
20 – 39	20.31	24.60
40 – 59	52.73	28.40
>60	26.96	28.50
Education level		
Still in education	2.12	3.50
No general education qualification ¹	0.77	4.00
Lower secondary education	2.44	35.10
Upper secondary education	32.39	23.50
Higher education ²	62.13	33.50
Missing	0.15	0.40

¹ includes primary education; ² includes postsecondary, tertiary education, bachelor, master and doctoral. NAKO sample and Mikrozensus (Bundesinstitut für Bildung und Forschung, 2025; DESTATIS, 2025b).

6.2. Methods and Statistical Analysis

6.2.1. Study I: Sporadic Use of Antibiotics in Older Adults and the Risk of Dementia: A Nested Case – Control Study Based on German Health Claims Data

The study used AOK data sample A, which was described in detail in Section 6.1.1. The sample included individuals who were 60 years or older and excluded individuals with a valid dementia diagnosis between 2004 and 2005 (see Section 6.1.1. for the definition of a valid dementia diagnosis). All patients were censored at the time of death, change of insurer, end of 2018, or the time of the first prescription of aminoglycoside antibiotics (J01G), a combination of antibiotics (J01R), or other antibiotics (J01X). The data sample included 153,697 individuals, of whom 35,072 had been diagnosed with dementia between the beginning of 2006 and the end of 2018. The observation ended with the date of the first dementia diagnosis. Each dementia patient was matched with two control individuals without dementia. For this, a matched incidence density sampling by age, sex, and observation time was used.

The analysis sample for the nested case-control study consisted of 105,216 individuals in total, with 35,072 dementia cases and 70,144 matched controls. Sporadic antibiotic use was considered up to the quarter of the dementia diagnosis; controls were followed up to the index date due to the matching procedure. Sporadic antibiotic use was defined as at least one filled antibiotic prescription.

To analyze the risk of subsequent dementia with an antibiotic prescription, odds ratios were estimated using conditional logistic regression models (StataCorp., 2025). The models were estimated individually for each antibiotic group. The models were controlled for comorbidities, diagnosis at least for one bacterial infection/disease, nursing home, severe long-term care, hospitalization and for each of the other antibiotic groups.

6.2.2. Study II: Dementia as a predictor of palliative care: Uncovering patient patterns based on German claims data

The AOK data sample B described in Section 6.1.1 was used for the study. The sample consisted of deceased persons with an observation period of one year prior to death. Skin cancer patients were excluded from the sample because skin cancer can be detected and treated early through the statutory cancer screening program in Germany and morbidity and mortality are lower than for other types of cancer (Robert Koch-Institut und die Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V., 2023). We created two data samples. The outpatient palliative care sample consisted of 37,430 patients. Due to the unbalanced dataset with respect to inpatient palliative care cases, an up-sampling was performed. The sample for the analysis of inpatient palliative care consisted of 43,896 individuals.

For the machine learning approach, the study samples were split into training, test, and validation data, separated by outpatient and inpatient palliative care. The training sample comprised 60% of each study population and the test and validation samples comprised 20%. Both models (inpatient and outpatient) were trained on the training data set and validated by the validation data set to determine the optimal parameter values. Finally, the models with optimal parameter values were fitted to the test data.

Logistic regression model and discrete conditional inference survival forest (cforest) (Hothorn et al., 2006) were used to predict the probability of inpatient and outpatient palliative care. Logistic regression model and cforest were predicted individually and then averaged without weighting. The input data for these models consisted of one row per quarter.

To determine whether the likelihood of receiving palliative care was increased or decreased by the predicted characteristics, odds ratios (OR) were calculated using a logistic regression model (StataCorp., 2025) for each outcome, controlling for the top 20 predicted characteristics.

6.2.3. Study III: Exploring the Impact of Social Networks and Cognitive Function on Mortality in Older Adults: Insights from the German National Cohort (NAKO)

The data of the NAKO were used, including only individuals aged 60 years and older. The observation time started at the time of the baseline survey and ended at the time of death or at the end of the observation period on December 31, 2023. The data set included 55,178 individuals.

To examine the risk of social networks and cognition in relation to mortality, hazard ratios (HR) were estimated using Cox proportional hazards models (StataCorp., 2023). Stepwise-adjusted models were estimated for semantic memory, executive function, and social network index. Next, interaction terms between semantic memory and social network index as well as between executive function and social network index, were included in two separate models. Each interaction effect was estimated three times, each time with a different reference group: low cognition and social network index level I (Ref. 1), moderate cognition and social network index level I (Ref. 2), and high cognition and social network index level I (Ref. 3). Bonferroni-adjusted p-values were applied to adjust for multiple testing (Holm, 1979).

7. Summary of the Study Results

The following chapter summarizes the cohorts and highlights the most important findings from all three studies.

7.1. Study I: Sporadic Use of Antibiotics in Older Adults and the Risk of Dementia: A Nested Case–Control Study Based on German Health Claims Data

Study Cohort

The 35,072 cases and 70,144 controls were observed for a mean follow-up period of 5.67 years. The mean age was 81.55 years for cases and 81.33 years for controls, and 64.11% of the study population were women.

At the time of diagnosis, the dementia patients had a higher prevalence of antibiotic prescriptions (72.93%) than the control patients (69.85%). When analyzed by antibiotic subgroup, quinolones (J01M) and macrolides, lincosamides, and streptogramins (J01F) were the most frequently prescribed antibiotics in both the dementia patients and the control group (J01M: case 41.72%, control: 38.06%, $p < 0.001$; J01F: case 31.95%, control 32.04%, $p = 0.7613$).

Main Results

After adjustment for age, sex and Elixhauser Comorbidity Index patients of the total group of antibiotics (J01) revealed a higher risk of a subsequent dementia diagnosis (Table 5, Model 1). After adjusting for at least one bacterial infection or disease, the odds ratio decreased to OR = 0.93 (Model 2: 95% CI = [0.90; 0.96]). The findings remained consistent even when nursing home residency, severe long-term care, and hospitalization were included in the analysis (Model 3).

Model results of the individual subgroups of antibiotic prescriptions confirmed the results of a significantly reduced odds ratio with dementia, with the exception of sulfonamides and trimethoprim (J01E). The lowest risk of dementia was found in patients with a prescription for macrolides, lincosamides and streptogramins (J01F) (OR = 0.88, 95% CI = [0.85; 0.92]). The probability of a subsequent diagnosis of dementia decreased by 4% to 8% in the other antibiotic subgroups.

Table 5. Stepwise-adjusted odds ratio and 95% confidence intervals by prescribed antibiotics for incident dementia.

	Model 1			Model 2			Model 3		
	OR	95% CI		OR	95% CI		OR	95% CI	
Antibiotics for systemic use (J01)	1.04	1.01	1.07	0.92	0.89	0.95	0.93	0.90	0.96
Elixhauser comorbidity score	1.09	1.08	1.09	1.07	1.07	1.08	1.04	1.03	1.04
Diagnosis of at least one bacterial infection/disease				3.18	3.08	3.29	1.60	1.54	1.67
Nursing home							3.59	3.37	3.82
Severe long-term care							2.06	1.83	2.32
Hospitalization							6.44	6.19	6.70

OR, Odds ratio; CI, confidence interval. Model 1: adjusted for age, sex and Elixhauser comorbidity score. Model 2: adjusted for age, sex, Elixhauser comorbidity score and diagnosis of at least one bacterial infection/disease. Model 3: adjusted for age, sex, Elixhauser comorbidity score and diagnosis of at least one bacterial infection/disease, nursing home, severe long-term care and hospitalization. Source: AOK data 2006–2018.

A prescription of antibiotics for only one quarter is neither negatively nor positively associated with subsequent dementia diagnosis. Prescriptions for two quarters significantly reduce the subsequent risk of dementia. For two quarters of antibiotic prescriptions, the chance decreases by 6% (95% CI = [0.89; 0.99]) and decreases to 20% (95% CI = [0.76; 0.84]) for five or more quarters.

When analyzed by antibiotic subgroup, only macrolides, lincosamides and streptogramins (J01F) significantly reduced the chance of dementia from the first quarter onwards (Figure 9). All other antibiotic subgroups, except sulfonamides and trimethoprim (J01E) and quinolones (J01M), at least for a short quarterly number of one or two consecutive quarters with antibiotic prescription, reduced the risk of dementia.

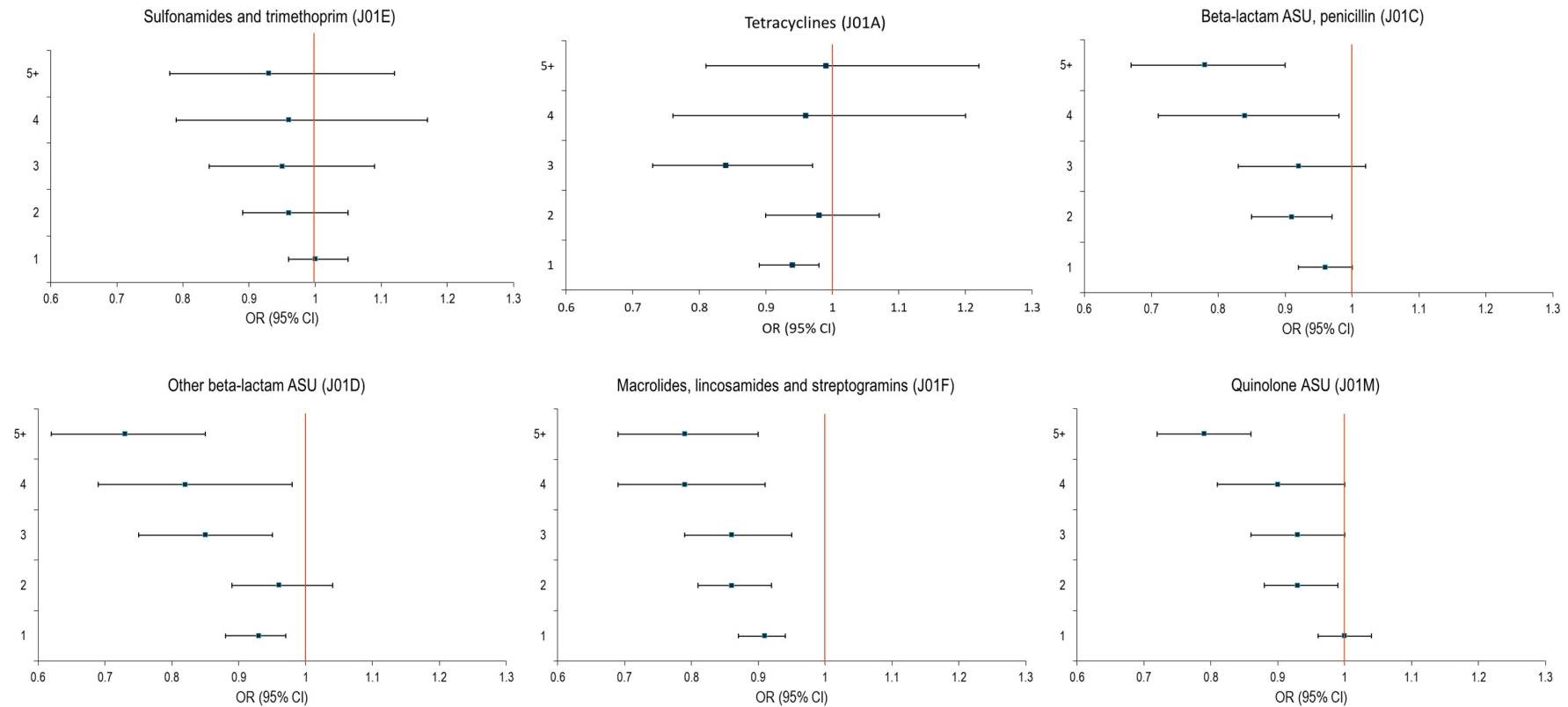


Figure 9. Odds ratio and 95% confidence intervals of cumulative number of quarters by prescribed antibiotic subgroups for incident dementia. OR, Odds ratio; CI, confidence interval. All models were adjusted for age, sex, Elixhauser comorbidity score, diagnosis of at least one bacterial infection/disease, nursing home, severe long-term care and hospitalization. Source: AOK data 2006-2018.

7.2. Study II: Dementia as a predictor of palliative care: Uncovering patient patterns based on German claims data

Study Cohorts

Inpatient Palliative Care

At the time of the prescription of inpatient palliative care, 48.43% of the patients were male and 51.57% female, with an average age of 74.83 years. At this time, 57.26% were diagnosed with cancer and 13.37% were diagnosed with dementia. Notably, 44.14% of patients with dementia received medications typically associated with dementia at that time. Furthermore, 34.43% of the patients had already received outpatient palliative care, while 18.07% were residing in nursing homes.

Outpatient Palliative Care

At the time of the outpatient palliative care prescription, the demographic composition of the patient sample was as follows: 41.87% of patients were male, and 48.13% were female. The mean age of the patients was 79.46 years, which is higher than the mean age for inpatient care. The most prevalent diagnosis, as previously reported, was cancer (41.57%), followed by dementia (30.77%). A substantial proportion of the inpatient care population had previously received care interventions. Long-term care accounted for 23.51% of cases, while nursing home stays constituted 38.55%.

Main Results

Inpatient Palliative Care

Among the 20 most important predictors for the prediction were primarily comorbidities (eight out of twenty variables were comorbidities). The time since the start of the observation period is the most important predictor for inpatient palliative care (Figure 10). The second and third most important variables were cancer diagnosis and age at baseline. The diagnosis of dementia and dementia medications were identified as important predictors. In addition, the following care measures are important for prediction: inpatient palliative care, doctor visits, and care in nursing homes, and are thus even more important than long-term care and the number of hospital days.

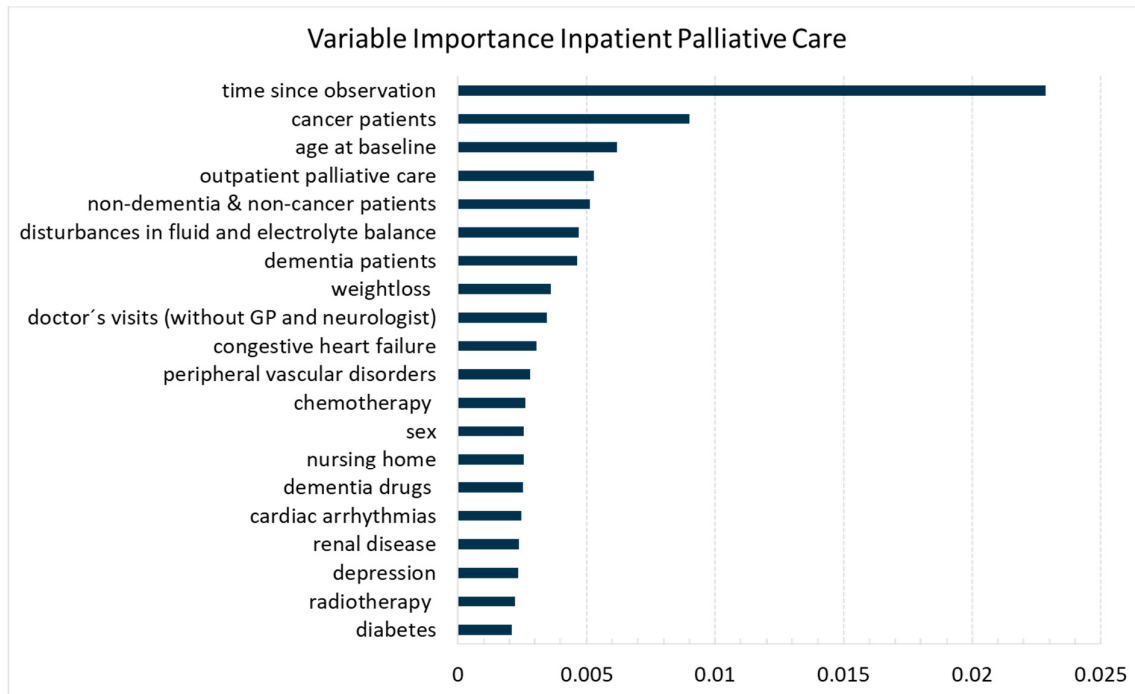


Figure 10. Variable importance for the model of inpatient palliative care. Source: AOK data 2014 – 2019.

Dementia patients had a significantly lower probability of receiving inpatient palliative care compared to cancer patients (OR = 0.28, 95% CI = [0.26; 0.30]) as well as the other patient groups (Table 6). The risk is increased mainly by comorbidity characteristics, but also by medical interventions and medications such as dementia medications, chemotherapy, and radiotherapy. Different associations were found for care interventions. Patients with outpatient palliative care had a 65% higher risk of inpatient palliative care, while nursing home residents had a lower risk (OR = 0.73, 95% CI = [0.68; 0.77]).

Table 6. Odds ratios from logistic regression with inpatient palliative care as outcome.

	Odds Ratio	P>z	[95% Conf. Interval]	
Demographics				
Time since observation	1.71	<0.001	1.67	1.74
Age at baseline	0.99	<0.001	0.98	0.99
Sex				
Male	Ref			
Female	1.16	<0.001	1.11	1.22
Patients group				
Cancer patients	Ref.			
Dementia patients	0.28	<0.001	0.26	0.30
Non-dementia & non-cancer patients	0.30	<0.001	0.29	0.32
Cancer & dementia patients	0.61	<0.001	0.56	0.67
Dementia & subsequent cancer patients	0.70	<0.001	0.60	0.82
Cancer & subsequent dementia patients	0.58	<0.001	0.51	0.67
Comorbidities				
Disturbances in fluid and electrolyte balance	1.35	<0.001	1.29	1.42
Weight loss	1.35	<0.001	1.28	1.42
Congestive heart failure	0.85	<0.001	0.81	0.90
Peripheral vascular disorders	1.13	<0.001	1.08	1.18
Cardiac arrhythmias	0.93	0.005	0.89	0.98
Renal disease	0.97	0.209	0.92	1.02
Depression	1.10	<0.001	1.05	1.15
Diabetes	0.99	0.538	0.94	1.03
Therapeutic remedies and rehabilitation				
Doctor’s visits (without GP and neurologist)	1.01	<0.001	1.01	1.01
Care interventions				
Outpatient palliative care	1.65	<0.001	1.56	1.73
Nursing home	0.73	<0.001	0.68	0.77
Medical interventions and major medications				
Chemotherapy	1.51	<0.001	1.41	1.61
Dementia medications	1.10	<0.001	1.05	1.15
Radiotherapy	2.95	<0.001	2.69	3.24

Controlled for the top 20 predictors. Source: AOK data 2014 - 2019.

Outpatient Palliative Care

The variable importance indicated that the time since the observation was the most important predictor (Figure 11). This was followed by non-dementia and non-cancer diagnosis, and cancer diagnosis. Dementia patients and patients with both dementia and cancer were also among the top 20 predictors. Pre-existing long-term care or nursing home residents, and patients with inpatient palliative care were identified as important predictors.

The probability of outpatient palliative care decreased significantly for dementia patients (OR = 0.33, 95% CI = [0.31; 0.36]) compared to cancer patients (Table 7). The combination of a cancer and dementia diagnosis and cancer and subsequent dementia patients also significantly reduced the risk compared to a cancer diagnosis alone (dementia patients: OR = 0.64, 95% CI = [0.59; 0.70]; cancer and subsequent dementia patients: OR = 0.54, 95% CI = [0.48; 0.62]). Care interventions such as long-term care and inpatient palliative care increased the risk by more than 93% and 97%, respectively. Nursing home residents had a 49% higher risk of outpatient palliative care.

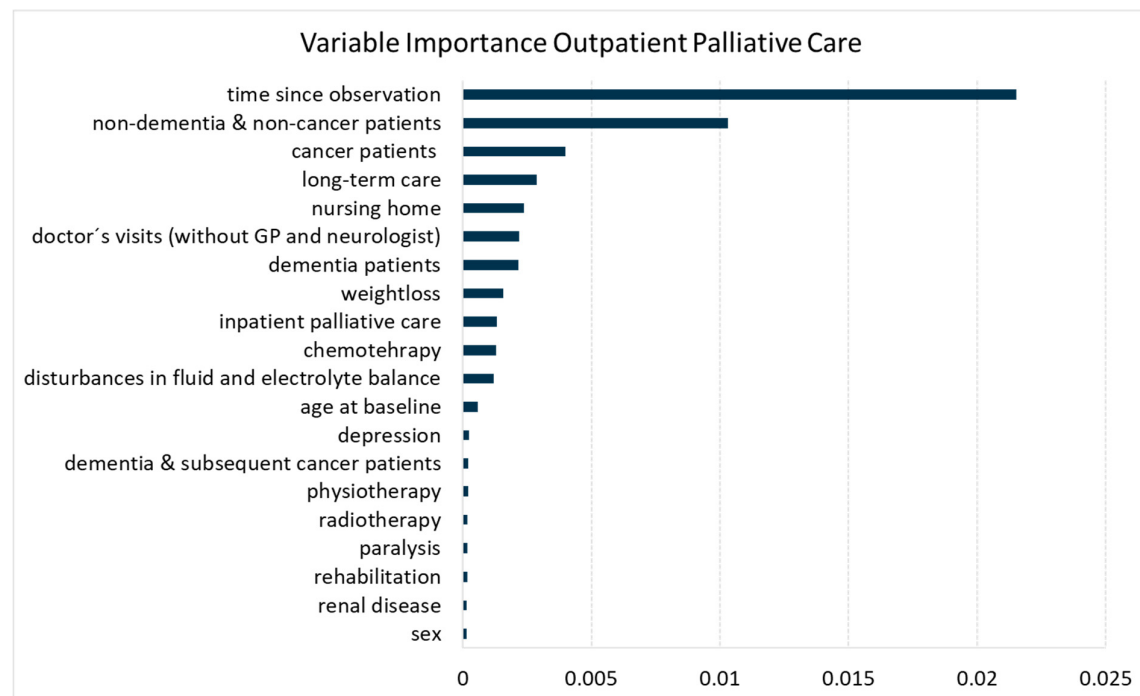


Figure 11. Variable importance for the model of outpatient palliative care. Source: AOK data 2014 – 2019.

Table 7. Odds ratios from logistic regression with outpatient palliative care as outcome.

	Odds Ratio	P>z	[95% Conf. Interval]	
Demographics				
Time since observation	1.46	<0.001	1.44	1.49
Age at baseline	1.00	0.002	1.00	1.01
Sex				
Male	Ref.			
Female	1.12	<0.001	1.07	1.17
Patient groups				
Cancer patients	Ref.			
Dementia patients	0.33	<0.001	0.31	0.36
Non-dementia & non-cancer patients	0.18	<0.001	0.17	0.19
Cancer & dementia patients	0.64	<0.001	0.59	0.70
Dementia & subsequent cancer patients	1.00	0.954	0.88	1.15
Cancer & subsequent dementia patients	0.54	<0.001	0.48	0.62
Comorbidities				
Weight loss	1.57	<0.001	1.50	1.65
Disturbances in fluid and electrolyte balance	1.39	<0.001	1.33	1.46
Depression	1.17	<0.001	1.11	1.22
Paralysis	1.07	0.025	1.01	1.13
Renal disease	1.00	0.856	0.96	1.05
Therapeutic remedies and rehabilitation				
Doctor’s visits (without GP and neurologist)	1.03	<0.001	1.03	1.03
Physiotherapy	1.09	0.002	1.03	1.15
Rehabilitation	1.58	<0.001	1.38	1.82
Care interventions				
Long-term care	1.93	<0.001	1.83	2.05
Nursing home	1.49	<0.001	1.41	1.57
Inpatient palliative care	1.97	<0.001	1.82	2.13
Medical interventions and major medications				
Chemotherapy	2.05	<0.001	1.89	2.23
Radiotherapy	1.57	<0.001	1.38	1.80

Controlled for the top 20 predictors. Source: AOK data 2014 - 2019.

7.3. Study III: Exploring the Impact of Social Networks and Cognitive Function on Mortality in Older Adults: Insights from the German National Cohort (NAKO)

Study Cohort

The sample included 49.91% male and 50.09% female participants. At the baseline assessment, the majority of participants exhibited a social network index of II and III (30.00% and 32.43%, respectively), while 7.94% had the lowest level I. A smaller percentage of participants had a level of IV (2.53%). Most individuals had moderate performance in both semantic memory (63.21%) and executive function (68.96%). However, 6.69% had missing values in semantic memory, and 7.55% had missing values in executive function.

Main Results

Full adjusted Cox proportional hazard models revealed a significant reduction in mortality risk for individuals with moderate and high executive function compared with those with low executive function (high: HR = 0.72, 95% CI = [0.64; 0.81]; moderate: HR = 0.67, 95% CI = [0.55; 0.81]). However, no significant results were found for semantic memory functions. Figure 12 displays the hazard ratios of the interactions between cognitive domains and social network index. A notable pattern emerged in the interactions: a U-shaped risk curve, where combinations with the extreme levels (levels I and IV) exhibited a higher mortality risk compared to the moderate levels (levels II and III). Specifically, the combinations involving social network index level III demonstrated a significant reduction in mortality risk, particularly in combination with semantic memory (low: HR = 0.46, 95% CI = [0.33; 0.65]); moderate: HR = 0.72, 95% CI = [0.59; 0.88]; high: HR = 0.56, 95% CI = [0.37; 0.86]). This U-shaped pattern was absent in individuals with high executive function.

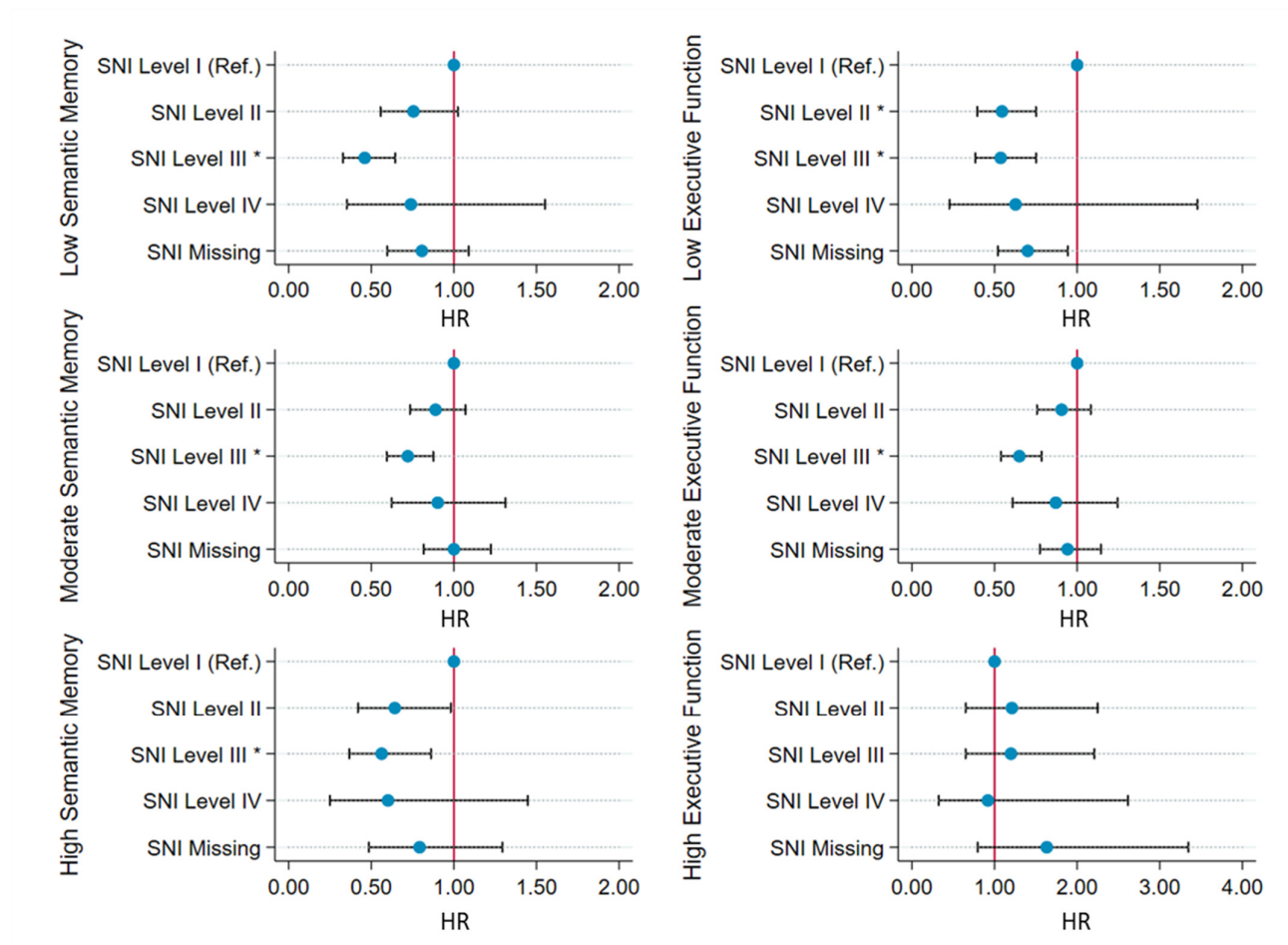


Figure 12. Hazard ratio and 95% confidence intervals of the same interaction term applied three times between cognition domains and social network index. HR, hazard ratio; CI, confidence interval; * significant after Bonferroni correction for testing three times. All models were adjusted for age, sex, study center, comorbidity Index, education, employment status, mother tongue, smoker status, alcohol consumption, physical activity and BMI. Source: NAKO baseline data and mortality follow-up. * significant after Bonferroni correction. SNI = Social network index. Source: NAKO data (2014-2023).

8. Discussion

The aim of this work was to find out what health care for dementia patients in old age and at the end of their lives looks like and how social networks affect these patients, in order to identify gaps in care and answer open questions about the current care structure. In view of the results, further discussion is needed in the context of the dementia process, the transferability of the results and for further research.

The path from a healthy state to the pathology of dementia and from the initial pathology to disability was examined in Study I. It was shown that systemic antibiotic treatment can attenuate the infectious inflammatory process and thus slow down the progression to clinically measurable dementia symptoms in old age. The effects of the various treatments with their different modes of action and antimicrobial spectra, as well as their different distribution kinetics, are associated with a reduction in the risk of dementia. The results are consistent with previous studies that have shown a positive effect of antibiotics on cognitive function (Loeb et al., 2004). The effect could be due to the control of pathogenic bacterial infection and the suppression of infection-related systemic inflammatory processes (Alam et al., 2017; Balducci & Forloni, 2019; Pradhan et al., 2016; Yaffe et al., 2003). Inflammatory episodes caused by infection accelerate the processes underlying cognitive dysfunction and cognitive decline. This supports the hypothesis that infections accelerate cognitive decline in individuals with or without clinical symptoms and are thus associated with an increased risk of dementia, regardless of their severity (Muzambi et al., 2021; Shah et al., 2013; Yaffe et al., 2003).

The specific examination of antibiotic use and the subsequent risk of dementia showed that the observed association was no longer positive but slightly negative when the infections themselves were included in the analysis. Consequently, infections, not antibiotics, may be the determining factor for an increased risk of dementia. This pathogenetic approach underscores the importance of regularly re-evaluating potential risk factors to weigh benefits and risks in the context of other preventable risk conditions. The relevance of a differentiated risk-benefit assessment of health services was emphasized and the generalization of known risks was put into perspective.

These findings are valuable for the use of health services. Understanding and knowledge of the benefits and effects of health interventions support their use. This is illustrated by the example of antibiotic prescriptions in the European region: there is a high level of unawareness among the population about the correct use and the effectiveness of antibiotics (Raupach-Rosin et al., 2019). Surveys have revealed worrying patterns of antibiotic use (Raupach-Rosin et al., 2019; World Health Organization, 2023b). Antibiotics have been taken without a doctor's prescription by around 8% of individuals (World Health Organization, 2023b). Only 16% of the individuals were aware of the correct way to handle antibiotics.

All of this raises the risk of antibiotic resistance (World Health Organization, 2025). According to the WHO, one of the greatest threats to health is posed by resistance (World Health Organization, 2023b). It is estimated that 4.71 million deaths worldwide in 2021 were associated with bacterial resistance (Naghavi et al., 2024). Forecasts indicate that by the year 2050, bacterial resistance could cause 8.22 million deaths worldwide (Naghavi et al., 2024).

Communicating knowledge about the effectiveness, consequences and appropriate use of health services can help to reduce health risks and promote responsible use of the healthcare system. An informed population uses health services more consciously and purposefully, avoiding unnecessary use and overuse. This can reduce the burden on health service providers in a sustainable way.

Study II focused on the state of existing impairment and disability from dementia and highlighted that, in addition to the known predictors of palliative care prescription (cancer diagnosis), unknown factors such as a dementia diagnosis were also important predictors. However, patients with dementia have a significantly lower probability of palliative care prescription compared to cancer patients, which supports the existing literature on the patient situation in Germany, where cancer patients still make up the largest proportion of palliative care patients (Stiel et al., 2010).

The data-driven approach to analyzing predictors highlights the importance of re-analyzing and re-evaluating known health services to uncover new, previously unknown predictors and to identify them as risk and protective factors.

Recognizing relevant diagnoses and comorbidities as previously unknown predictors highlights the relevance of palliative care not only for cancer patients as well as for other morbid patient groups at the end of life. Due to a lack of guidelines and indications for palliative care beyond cancer diagnosis, many patients have difficulty accessing palliative care (Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde et al., 2016). Lack of communication and knowledge about palliative care, as well as the stigma as an intervention for the dying, are barriers that can prevent access to palliative care (Ziehm et al., 2016). In view of the growing population and demographic change, the number of patients with a need for palliative care will also increase in the coming decades, which will pose major challenges for healthcare systems.

Regarding the growing number of dementia patients and the growing need for medical and nursing care in general (DESTATIS, 2023b, 2023d), it is becoming increasingly important to close care gaps and create access to care options. The number of middle-aged adults will decrease (DESTATIS, 2019), potentially reducing the amount of informal care that can be provided, and medical care will become even more important. The analysis and evaluation of the “actual state” is immeasurable in order to

advance medical care in the future and improve access, especially for patients who are not considered in the current care guidelines.

Study III examined the pathway from cognitive impairment in old age to death. The finding of a U-shaped risk pattern in the interaction of cognition and social networks on mortality risk suggests that moderate social integration may be particularly beneficial for old individuals, as it has the greatest impact on reducing mortality risk. The results emphasize the importance of promoting protective factors (social network integration) for old morbid population groups in order to reduce mortality risk. The combined risk of risk factor (low cognition) and the absence of protective factor (high social integration) exceeds the individual risks of each factor. This pattern was not seen in individuals with high executive function.

An influence of high social network integration on the association between cognition and mortality could not be demonstrated. This raises the question of what other factors or mechanisms could influence the relationship between social integration, cognitive function and mortality. One possible explanation could be traced back to the morbidity structure of the individuals, in which individuals with high social integration were already seriously ill and, due to their state of health and need for support, already had a strong social network that took care of them. The presence of very serious illnesses such as severe cognitive impairment or dementia, but also of comorbidities such as cardiovascular diseases, increases the risk of mortality (Alzheimer's Association, 2025; Rodgers et al., 2019) and cannot be reduced even by a strong social network.

Furthermore, networks with many different groups of people can result in too many social contacts for one person. While interpersonal relationships generally help to manage stress, an excessive number of interactions can cause social stress (Bisschop et al., 2003). Having a large number of contacts can weaken the bond with individuals, resulting in a network dominated by superficial relationships rather than close ones. These relationships tend to offer less support in everyday life and only short-term care. Since there is a reduced risk of mortality, albeit non-significant, it is important to clarify the mechanism and identify possible protective factors. This should be investigated in future research.

The analysis underscores the importance of analyzing protective factors in the context of existing risk factors, especially at the end of life, and of uncovering mechanisms of effect. More differentiated insights into the interrelationships provide information on the extent to which protective factors are effective and when their effect reaches its limits, in order to delay the process from impairment/disability to death. With the growing demand for care support, social networks offer the potential to reduce the burden on the healthcare system in the future.

Strengths and Limitations of the Underlying Studies

With the AOK data from around 250,000 insured persons per sample, studies I and II benefited from comprehensive data collected from the inpatient and outpatient sectors, including nursing homes in Germany. The standardized data collection reduces problems such as selection and recall bias. Earlier studies (Fink, 2014, 2017) and comparisons of the death rates (Section 6.1.1) conducted for this thesis also showed the representativeness of the study population in relation to mortality in the German population. The routinely collected data provides information on the insured over a period of 13 years, which made it possible to show the development of illness and the need for care in a longitudinal section and to make statements about the individual and social consequences of aging.

However, the data are used primarily for administrative purposes, which limits the generalizability of the results. Sociodemographic and socioeconomic information is lacking. Furthermore, the AOK has a higher proportion of individuals with low socioeconomic status compared to other public health insurance funds and compared to private health insurance companies in Germany (Epping et al., 2021). These differences may impact morbidity and health care utilization, but are partly explained by the different age distribution within the AOK population, which is older than the general German population.

Claims data and dementia registries are valuable for tracking dementia, but the average delay in dementia diagnosis in registry data is about 5.5 years (Rizzuto et al., 2018). Dementia is a progressive disease that begins years before the first clinical symptoms, so patients may appear healthy in the data even though they are already suffering from the onset of cognitive changes. Furthermore, diagnoses are only recorded when insured persons come into contact with the healthcare system and consult a doctor. This can lead to lower incidence and prevalence estimates due to a possible distortion in reporting. A previous analysis addressed this issue and demonstrated that the dementia prevalence in the data is comparable to other population-based studies (Doblhammer et al., 2015).

The data includes health claims information for the health care services but not the information on the actual use of prescribed therapies and medications, which may result in an overestimation of the actual services. However, the adherence of patients to antibiotic therapies, which is relevant to Study I, is estimated to be good (Raupach-Rosin et al., 2019). When analyzing other therapies or services, patient adherence should always be considered and checked.

Study II used the log-loss metric based on cross-entropy to measure prediction quality. However, tuning regarding the c-index resulted in a loss of calibration. Therefore, the combined logistic regression and cforest model was selected as a compromise between the c-index and calibration model coefficients. The data included a limited number of outpatient cases, so up-sampling was

performed beforehand. Potential data-related issues affecting the prediction of outpatient palliative care should be considered. In order to make accurate predictions about outpatient palliative care, it is necessary to use prediction models with more suitable data.

The structure of the claims data leads to truncation and censoring (Weißbach et al., 2024; Weißbach et al., 2021), because the data contain incomplete information before the start of the observation period and missing information after the end of the observation period. Therefore, an underestimation of both the new cases of dementia and the use of antibiotic treatments and palliative care must be considered.

The NAKO data is characterized by a large, comprehensive study population of 200,000 participants. The study is the largest cohort study and biobank in Germany and includes a wide range of information from the sociodemographic, socioeconomic and medical fields.

However, the study population is not representative of the German population and is potentially biased due to selection, as the study participants were comparatively better educated and healthier and represented only about 1/3 of the mortality rate (Section 6.1.2.). These sociodemographic characteristics were associated with a greater willingness to participate in health studies (Lindsted et al., 1996). The relatively healthy and active state of the study population tends to weaken the observed relationships rather than overestimate them. Generalizability was also limited by low response rates among participants, and estimates of risks, as well as disease and prevalence rates, are only partially transferable to the German population (Peters et al., 2022).

Validated neuropsychological test batteries allowed a meaningful assessment of cognition and its influencing factors (Kleineidam et al., 2023). However, the data collected on patient histories, lifestyle factors, and social integration are largely self-reported. This can lead to recall bias and social desirability bias (Nederhof, 1985; Prince, 2012), resulting in overestimation. Furthermore, social contacts were measured via family, friends and leisure groups; professional contacts were not considered. These could compensate for a lack of family contacts due to bereavement or relocation. The actual number of social contacts may have been underestimated. To counteract this, study III controlled for employment status.

A further potential limitation of our results arose from the mortality follow-up. Mortality queries were made at regular intervals to the registry offices as part of the mortality follow-up. Due to the time lag between the actual time of death and the time of the mortality query, individuals may have been classified as still living in the study even though they had already died. To address the problem of

misclassification of deaths and to ensure the most accurate classification possible, we limited the observation period to the end of December 2023.

A major strength of the data and for analyses will be the long-term collection of patient data over the next decades. The regular collection of health status, lifestyle factors, environmental exposures and social networks of the participants will provide a unique data source in terms of the scope and depth of information (German National Cohort (NAKO) Consortium, 2015; Peters et al., 2022). The planned linkage with secondary and registry data from the statutory and private health insurance funds, the Central Research Institute of Ambulatory Health Care in Germany, the German Federal Pension Insurance and other individual pension insurance providers, the Institute for Employment Research of the Federal Employment Agency, as well as the Epidemiological Cancer Registry and Clinical Cancer Registry offers a novel, unprecedented data source (NAKO Gesundheitsstudie, 2025).

Outlook

With the growing number of people with dementia and the associated increase in care, a focus on research into protective and risk factors is essential. As medicine and medical care continue to evolve, analyzing contributing factors is crucial. The relevance of the evaluation and assessment of risk factors is highlighted by the published Lancet Commission article (Livingston et al., 2020). The revision of known risk factors and the new classification of these factors illustrates the relevance of ongoing research into risk and protective factors.

In the future, the NAKO data will provide an extensive view of risk and protection factors from a medical as well as a sociodemographic and socioeconomic perspective. The planned linking with secondary and registry data will enable a holistic view of patients and enable analyses that include information from all relevant sub-areas such as medicine, environment and lifestyle. Regularly repeated surveys enable in-depth phenotyping and the assessment of disease development and multimorbidity in an aging society (German National Cohort (NAKO) Consortium, 2015).

The AOK data have already proven to be a suitable data source for the prediction of inpatient palliative care and dementia (Rakuša et al., 2025; Reinke, 2025). Since the utilization of palliative care depends not only on a patient's medical history, but also on family structures and individual health beliefs, analyses using the NAKO data enable new insights into potential predictors for palliative care and other health services that have not been previously identified. Barriers and gaps in the provision of various health services can be identified for patient groups. This knowledge can improve patient care and make it more efficient, ultimately saving resources and costs in the healthcare system.

9. Conclusion

The findings of this thesis can be summarized as follows:

- Sporadic antibiotic prescriptions (excluding sulfonamides and trimethoprim (J01E)) in old age reduces the subsequent risk of dementia, which may be due to the attenuation of an infectious inflammatory process, which in turn may delay the process of neurodegeneration (Study I).
- The pathogenetic approach of the relationship between risk factors and the development of the disease underlines the importance of investigating risk factors in the transition from a healthy state to dementia. Furthermore, it is important to regularly reevaluate potential risk factors to weigh benefits and risks in the context of other preventable risk factors in old age.
- A dementia diagnosis, similar to a cancer diagnosis, is predictive of palliative care, although patients with a diagnosis of dementia appear to have a much lower probability of receiving palliative care (Study II).
- Analysis of predictors underscores the importance of further analyzing and evaluating known health services to uncover new or previously less relevant predictors and to identify risk and protective factors at the end of life.
- The interaction of cognition and social network integration on mortality revealed that moderate social integration is especially beneficial (Study III).
- The analysis underscores the relevance of analyzing protective factors in the context of existing risk factors in old age in order to uncover new, previously unknown interactions. More differentiated insights into the relationships provide information on the extent to which protective factors are effective and where their effect shows limits, in order to delay the process of cognitive impairment leading to death.

This thesis emphasizes the importance of regular examination and evaluation of risk and protective factors in the course of dementia. The lack of treatment options continues to focus attention on the prevention and delay of dementia.

Interventions for the prevention and care of dementia patients play an important role at every stage of the disease. Knowledge about adequate care options and the effect and benefits of care services offers the potential for patients to make more careful use of health services, for avoiding resistance to medication, for reducing the excessive workload on health care providers and for cutting costs resulting from unnecessary contacts with the healthcare system.

Filling gaps in care and reducing barriers to care also reduces the burden on the public health system by speeding up patient access to care and slowing the progression of disability. Costly treatments due

to advanced disease and associated side effects can be reduced. Previously unimportant predictors are becoming more relevant due to demographic changes and continuous advances in medicine and prevention. Guidelines can be updated through regular re-evaluation and patient groups not previously considered can be identified.

The growing number of older people in the population in the coming decades will pose a challenge to public health because of the increase in age-related diseases and the need for support. This makes social integration and the resulting opportunity for support in everyday life outside of medical care even more relevant. In addition, social interaction has a positive effect on the decline of cognitive functions and delays the process of disability.

Consequently, the knowledge on risk and protective factors presented here can help to ensure that people in old age receive better care, thereby reducing the risk of dementia and providing appropriate treatment for those already suffering from dementia. The findings not only contribute to the course of dementia, but also apply to successful aging in general and can be transferred to other progressive diseases. All patients, regardless of their disease, need access to medical care and integration into social networks. Promoting these factors will contribute to successful aging and good care for all patients in old age and at the end of life.

10. References

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11. Original Publications

Study I

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Sporadic Use of Antibiotics in Older Adults and the Risk of Dementia: A Nested Case–Control Study Based on German Health Claims Data

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Abstract.

Background: Antibiotics for systemic use may increase the risk of neurodegeneration, yet antibiotic therapy may be able to halt or mitigate an episode of neurodegenerative decline.

Objective: To investigate the association of sporadic use of antibiotics and subsequent dementia risk (including Alzheimer's disease).

Methods: We used data from the largest public health insurance fund in Germany, the Allgemeine Ortskrankenkasse (AOK). Each of the 35,072 dementia cases aged 60 years and older with a new dementia diagnosis during the observation period from 2006 to 2018 was matched with two control-patients by age, sex, and time since 2006. We ran conditional logistic regression models for dementia risk in terms of odds ratios (OR) as a function of antibiotic use for the entire antibiotic group and for each antibiotic subgroup. We controlled for comorbidities, need for long-term care, hospitalizations, and nursing home placement.

Results: Antibiotic use was positively associated with dementia (OR = 1.18, 95% confidence interval (95%CI): 1.14–1.22), which became negative after adjustment for comorbidities, at least one diagnosis of bacterial infection or disease, and covariates (OR = 0.93, 95%CI: 0.90–0.96). Subgroups of antibiotics were also negatively associated with dementia after controlling for covariates: tetracyclines (OR = 0.94, 95%CI: 0.90–0.98), beta-lactam antibacterials, penicillins (OR = 0.93, 95%CI: 0.90–0.97), other beta-lactam antibacterials (OR = 0.92, 95%CI: 0.88–0.95), macrolides, lincosamides, and streptogramins (OR = 0.88, 95%CI: 0.85–0.92), and quinolone antibacterials (OR = 0.96, 95%CI: 0.92–0.99).

Conclusion: Our results suggest that there was a decreased likelihood of dementia for preceding antibiotic use. The benefits of antibiotics in reducing inflammation and thus the risk of dementia need to be carefully weighed against the increase in antibiotic resistance.

Keywords: Alzheimer's disease, antibiotics, conditional logistic regression, dementia, epidemiology, nested case-control studies

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INTRODUCTION

As the elderly population increases, the number of dementia patients will also increase, as the strongest risk factor for developing dementia is advancing age [1, 2]. In 2019, approximately 55 million people worldwide were affected, and the number of dementia patients will increase rapidly; 40 percent more people are expected to be living with dementia in 2030 than today [1, 3]. Dementia is driving up care and health insurance costs, which increases costs for governments, communities, families, and individuals. This makes research on risk and protective factors an important step toward dementia prevention [1, 4, 5].

Many risk factors have already been identified [6], but only a few studies have explored the risk of the use of antibiotics for systemic use (ASU) on dementia incidence [7, 8]. ASUs eliminate the colonization of the human body with pathogenic bacteria and prevent systemic inflammation, and are thought to promote or maintain health [9]. However, they also affect the gut microbiome [10] and increase antimicrobial resistance, which can have an overall negative impact on the health of individuals and ultimately entire populations. They are effective against a broad spectrum of bacteria, act throughout the organism, and can be used in a variety of ways [11].

There are two competing hypotheses regarding the association between ASU and dementia incidence. On the one hand, ASU that act against a wide range of bacteria cause an unbalanced gastrointestinal microbiome because they affect the composition of the gut microbiota; they reduce its biodiversity and delay healthy, balanced bacterial colonization of the gut over a long period of time [7, 12–14]. Antibacterial-induced dysbiosis of the microbiome can have a direct and indirect, as well as short- and long-term, impact on health [12, 14, 15]. Modifications of the gut microbiome are associated with cognitive function and various neurological and neurodegenerative diseases, and the microbiome can influence the brain and neurological activities as well as causing possible memory impairment and dysfunction [7, 16, 17]. Thus, the use of ASU could be associated with an increase in dementia risk.

On the other hand, pathological changes in the brain and cerebral immune responses are intimately involved both in infectious delirium and Alzheimer's disease [18]. There is strong evidence that most neurodegenerative diseases are propelled by systematic

inflammation caused by peripheral infections such as bacterial sepsis, periodontitis but also autoimmune disease all of which are able to drive an activation of local immune responses in the brain [19–26]. Infection-related episodes of inflammation, particularly in the elderly, exacerbate processes in the brain that underlie cognitive decline, meaning that infections can accelerate cognitive decline in people with, but also without, clinical symptoms [19]. ASU treatment could attenuate the infectious inflammatory process, thereby decelerating the process to clinically measurable symptoms of dementia [22] and reducing the dementia risk [27]. Thus, the use of ASU should be associated with a decrease in dementia risk.

We tested these two competing hypotheses by conceiving a nested case-control study using German health claims data. We examined the risk of incident dementia in patients who had filled at least one ASU prescription compared to those without.

METHODS

Analysis sample

We used a random longitudinal sample of 250,000 insurants of Germany's largest public health insurance fund, the Allgemeine Ortskrankenkasse (AOK). The sample was drawn in the first quarter of 2004 and followed quarterly through the end of 2019. The data provide demographic information about sex, year and month of birth, month and year of death (if applicable), the place of residence, and whether the person lived in an institution or not. Furthermore, the sample includes information on all inpatient and outpatient diagnoses, coded according to the German modification of the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10). The data contain filled prescriptions of drugs coded according to the Anatomical Therapeutic Chemical Classification (ATC) code of active ingredients and drugs.

We included individuals who were born before 1945, excluding individuals with a valid dementia diagnosis in 2004 and 2005. By using a two-year washout period, we attempted to approximate incident dementia cases. All patients were censored at the time of death, at change of insurer, or at the end of 2018 (to permit the validation of dementia diagnoses). We also censored at time of the first filled prescription with aminoglycoside ASU (J01G), combinations of ASU (J01R), and other ASU (J01X)

because very few patients were prescribed these ASU. Of the 250,000 individuals in our original sample, 153,697 individuals were included in our data sample according to our inclusion criteria. 35,072 individuals had diagnosed dementia between the beginning of 2006 and the end of 2018. The observation ends at the time of the first dementia diagnosis. Details of the exclusion criteria are available in Supplementary Figure 1. All subgroups of ASU included are described below under “Definition of antibiotics for systemic use”.

Study design

For our nested case-control study, using incidence-density sampling (Stata command `sttocc`), we matched each incident dementia case to two controls without dementia by age (in five-year groups), sex, and time since 2006 to minimize bias in using cases and controls with different follow-up times [28]. For controls, the index date was set to the date of dementia diagnosis of the matched cases. Our final data sample consisted of 105,216 individuals, with 35,072 dementia cases through the end of 2018 and 70,144 matched controls. We considered the sporadic use of antibiotics until the quarter of dementia diagnosis, controls until the index date due to the matching process. Sporadic antibiotic use is defined as at least one filled ASU prescription.

Definition of dementia

We used the following ICD-10 codes to define dementia: dementia in AD (F00), vascular dementia (F01), dementia in other diseases classified elsewhere (F02), unspecified dementia (F03), delirium superimposed on dementia (F05.1), Alzheimer dementia (G30), and circumscribed brain atrophy (G31.0). To avoid the problem of false-positive diagnoses, we used an established internal two stage validation strategy [29, 30]. First, we only used labeled outpatient diagnoses as verified by medical doctors, and inpatient discharge and secondary diagnoses. In the next stage, we considered diagnoses valid if they were confirmed by a concurrent inpatient and outpatient diagnosis and by two diagnoses from two different types of physicians within the same quarter. If a person died within the same quarter in which the dementia was first diagnosed, a diagnosis was still considered to be valid.

Definition of antibiotics for systemic use

We used the following ATC-codes to identify the following prescribed ASU (J01): tetracyclines (J01A), beta-lactam ASU (J01C), other beta-lactam ASU (J01D), sulfonamides and trimethoprim (J01E), macrolides, lincosamides, and streptogramins (J01F), and quinolone ASU (J01M).

Covariates

The comorbidity burden was calculated using the Elixhauser comorbidity score, which includes 30 diseases [31]. We combined the occurring comorbidities into a total score so that the burden of disease could be assessed with a single numeric score. Furthermore, we controlled for diseases and bacterial infections usually treated with ASU, such as gastrointestinal infections (A00-A09), pneumonia (J1[J234678], J110, J84, J150-J159, P23[012345689], P350), respiratory infection (H67, J01-J02, J200-J202), bladder and urinary tract infections (N30, N33, N37, N39), skin infections (L01, L02, L03, L08, A46) and for bacterial infections associated with an increased risk of cognitive impairment and dementia such as sepsis [32, 33], bacterial meningitis [34], meningococcal infection [35], and Lyme disease [36]. The diseases and bacterial infections were combined into one variable indicating whether or not a disease or bacterial infection was diagnosed in a specific quarter. We controlled whether or not patients lived in a nursing home and whether or not they had been hospitalized at least once since the start of observation. In addition, we controlled for the presence or absence of severe long-term care dependency, with severe long-term care dependency defined as care level 3 (up to the end of 2016) or care grade 5 (from 2017 onwards). More details are available in the Supplementary Method 1. For each subgroup of ASU, we created a dummy variable consisting of all the other remaining subgroups of ASU. This dummy variable indicates whether or not at least one of the remaining ASU was filled in a pharmacy in the current quarter. Additionally, we included age on a continuous scale. All predictors except age were coded as time-dependent binary variables with a value of one from the first occurrence onward and zero otherwise. We measured the covariates for cases at the time of dementia diagnosis and for control subjects at the index date.

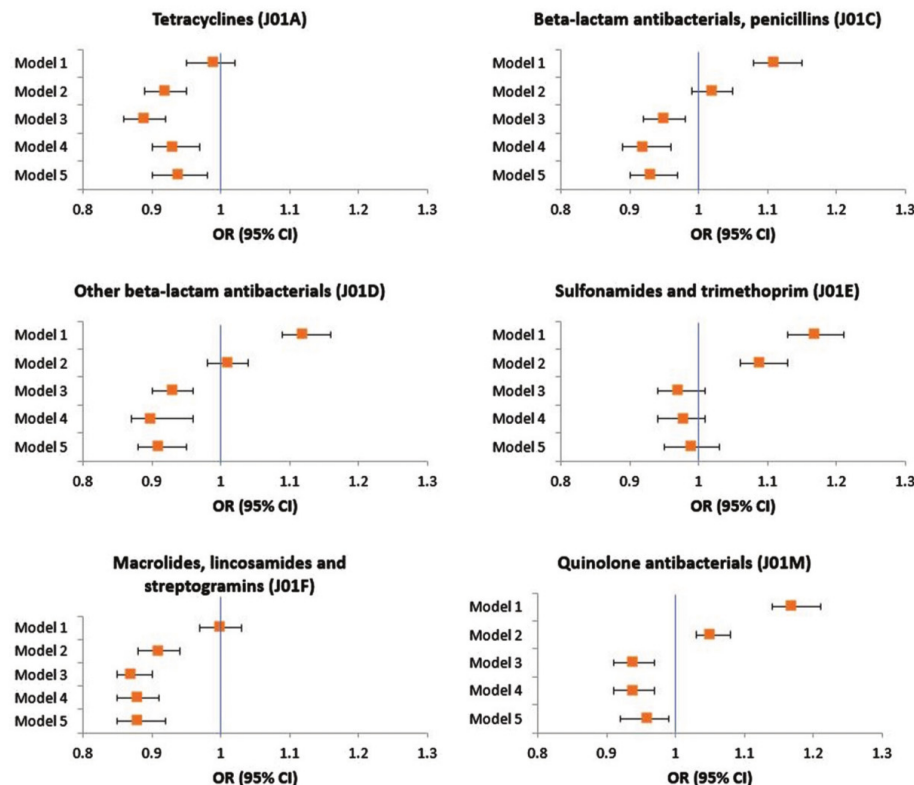


Fig. 1. Stepwise-adjusted odds ratio and 95% confidence intervals by prescribed antibiotics for incident dementia. N = 105,216; OR, Odds ratio; CI, confidence interval; ASU, antibiotics for systemic use. Model 1: adjusted for age and sex. Model 2: adjusted for age, sex and Elixhauser comorbidity score. Model 3: adjusted for age, sex, Elixhauser comorbidity score, diagnosis of at least one bacterial infection/disease. Model 4: adjusted for age, sex, Elixhauser comorbidity score, diagnosis of at least one bacterial infection/disease and other control variables. Model 5: adjusted for age, sex, Elixhauser comorbidity score, diagnosis of at least one bacterial infection/disease, other control variables and the use of ASU of the other subgroup. Source: AOK data 2006–2018.

Analysis strategy and statistical methods

To examine the risk of dementia associated with ASU, we estimated odds ratios (OR) with conditional logistic regression models [37] for the total group of ASU, and for each of the six ASU groups separately.

First, crude models were estimated which controlled for age and sex due to the study design and for age on a continuous scale. Second, adjusted models were estimated by including the Elixhauser comorbidity score, diagnosis of at least one bacterial infection/disease, other control variables, and the other ASU. Third, lag-times of ASU use from one up

to three years were implemented, which measured the time since the first prescription of (the specific) ASU was filled. Fourth, the number of quarters with at least one filled prescription were included in the models by cumulating the number of quarters with ASU across all and across the specific groups of ASU.

As a sensitivity analysis, all analyses were performed for patients with diabetes only and only for patients living in nursing homes, as the risk of inflammation and dementia is particularly high in these patients [38, 39]. All analyses were performed using Stata 16.0.

Ethical approval

Access to the health claims data was granted and approved by the Scientific Institute of the AOK (WIdO), while access to the complete database was not possible, due to current data protection regulations. All analyses of this study are based on anonymized administrative claims data which never identify patients directly. As individuals are anonymous, the results presented here do not in any way affect the persons whose records were used. No ethical approval was required, therefore this study complies with the tenets of the Declaration of Helsinki.

RESULTS*Descriptive results*

Because of the matching process by age, sex, and follow-up time, the proportion of age and sex and the follow-up time were identical for cases and controls. Both the 35,072 cases and the 70,144 controls had a follow-up time of 5.67 years, the mean age was 81.55 years for cases and 81.33 years for controls, and 64.11% were women (Table 1). At the date of diagnosis, the prevalence of ASU was slightly but significantly higher among case than control patients, with 73% of case patients and 70% of control patients having filled an ASU (J01) (Table 1). Filled prescription of quinolone ASU (J01M) (Table 1, case 42%, control: 38%, $p < 0.001$), and macrolides, lincosamides, and streptogramins (J01F) were most frequent (Table 1, case 32%, control 32%, $p = 0.7613$); those of tetracyclines (J01A) the least frequent (Table 1, case: 18%, control 18%, $p = 358$). In terms of chronic diseases and infections the case group generally had a worse health profile than did the control group. In the case group there were more than three times as many gastrointestinal infections (Table 1, cases 4.76%, controls 1.19%, $p < 0.001$), pneumonia infections (Table 1, cases 7.42%, controls 2.260%, $p < 0.001$), and patients with severe long-term care (Table 1, cases 3.63%, controls 0.93%, $p < 0.001$) than in the control group. The proportions of people living in nursing homes (Table 1, cases 15.24%, controls 3.59%, $p < 0.001$) and those receiving inpatient care (Table 1, cases 49.36%, controls 10.48%, $p < 0.001$) were almost four times higher than in the control group.

*Model results**Total group of ASU (J01)*

For the total group of ASU, there was a positive association with a subsequent diagnosis of dementia after adjustment for age and sex (Table 2, model 1: OR = 1.18, 95% CI: 1.14–1.22). Further adjustment for the Elixhauser comorbidity score attenuated some of the positive association (Table 2, model 2: OR = 1.04, 95% CI: 1.01–1.07). After controlling for at least one bacterial infection or disease, the association became negative (Table 2, model 3: OR = 0.92, 95% CI: 0.89–0.95). Additional adjustment for other control variables did not change the association (Table 2, model 4: OR = 0.93, 95% CI: 0.90–0.96).

Subgroups of ASU

Adjusting for age and sex, there was an increased OR for preceding use of antibiotic subgroups beta-lactam antibiotics, penicillins (J01C), other beta-lactam antibiotics (J01D), sulfonamides and trimethoprim (J01E), and quinolone antibiotics (J01M) (Fig. 1, model 1: J01C: OR = 1.11, 95% CI: 1.08–1.15; J01D: OR = 1.12, 95% CI: 1.09–1.16; J01E: OR = 1.17, 95% CI: 1.13–1.21; J01M: OR = 1.17, 95% CI: 1.14–1.21). There were no significant associations for the other groups of ASU.

In addition, controlling for Elixhauser comorbidity score and the diagnosis of at least one bacterial infection or disease, there was a significantly decreased OR for all subgroups of ASU, except sulfonamides and trimethoprim (J01E), with dementia (Fig. 1, model 3: J01A: OR = 0.89, 95% CI: 0.86–0.92; J01C: OR = 0.95, 95% CI: 0.92–0.98; J01D: OR = 0.93, 95% CI: 0.90–0.96; J01E: OR = 0.97, 95% CI: 0.94–1.01; J01F: OR = 0.88, 95% CI: 0.85–0.90; J01M: OR = 0.94, 95% CI: 0.91–0.97). The association persisted after controlling for additional control variables. Additionally, we controlled each OR of the subgroups for the use of the other subgroups of ASU. The control does not change the association from the previous model (Fig. 1, model 5: J01A: OR = 0.94, 95% CI: 0.90–0.98; J01C: OR = 0.93, 95% CI: 0.90–0.97; J01D: OR = 0.92, 95% CI: 0.88–0.95; J01E: OR = 0.99, 95% CI: 0.95–1.03; J01F: OR = 0.88, 95% CI: 0.85–0.92; J01M: OR = 0.96, 95% CI: 0.92–0.99). A tabular overview of all OR is available in Supplementary Table 1A–F. We confirmed the results in sensitivity analyses with diabetic patients only and with nursing

Table 1
Characteristics of the study population

	Cases (N = 35,072)		Controls (N = 70,144)		Difference Case Control group <i>p</i>
	N	(%)	N	(%)	
ASU					
ASU (J01)	25,577	72.93	48,996	69.85	< 0.001
Tetracyclines (J01A)	6,361	18.14	12,885	18.37	0.358
Beta-lactam ASU, penicillins (J01C)	10,218	29.13	19,033	27.13	< 0.001
Other beta-lactam ASU (J01D)	8,423	24.02	15,497	22.09	< 0.001
Sulfonamides and trimethoprim (J01E)	7,232	20.62	12,775	18.21	< 0.001
Macrolides, lincosamides and streptogramins (J01F)	11,204	31.95	22,473	32.04	0.7613
Quinolone ASU (J01M)	14,633	41.72	26,694	38.06	< 0.001
Matching variables					
Age					1
60–64	225	0.64	450	0.64	
65–69	1,319	3.76	2,638	3.76	
70–74	4,201	11.98	8,402	11.98	
75–79	7,709	21.98	15,418	21.98	
80–84	9,377	26.74	18,754	26.74	
85–89	7,706	21.97	15,412	21.97	
90+	4,534	12.93	9,070	12.93	
Mean Age	81.55		81.33		
Sex					1
Male	12,588	35.89	25,176	35.89	
Female	22,484	64.11	44,968	65.11	
Elixhauser comorbidity score mean (sd)	7.89 (3.44)		6.85 (3.55)		< 0.001
Bacterial infections/diseases					
Gastrointestinal infections	1,668	4.76	836	1.19	< 0.001
Pneumonia	2,604	7.42	1,121	1.60	< 0.001
Respiratory infections	293	0.84	597	0.85	0.7935
Bladder and urinary tract infections	7,667	21.86	5,446	7.76	< 0.001
Skin infections	1,231	3.51	1,115	1.59	< 0.001
Bacterial infections associated with dementia	335	0.96	165	0.24	< 0.001
Other control variables					
Nursing home	5,346	15.24	2,515	3.59	< 0.001
Severe long-term care	1,272	3.63	651	0.93	< 0.001
Hospitalization	17,310	49.36	7,350	10.48	< 0.001

ASU, antibiotics for systemic use; sd, standard deviation. Source: AOK data 2006–2018.

Table 2
Stepwise-adjusted odds ratio and 95% confidence intervals by prescribed antibiotics for incident dementia

	Model 1			Model 2			Model 3			Model 4		
	OR	[95% CI]		OR	[95% CI]		OR	[95% CI]		OR	[95% CI]	
ASU (J01)	1.18	1.14	1.22	1.04	1.01	1.07	0.92	0.89	0.95	0.93	0.90	0.96
Elixhauser comorbidity score				1.09	1.08	1.09	1.07	1.07	1.08	1.04	1.03	1.04
Diagnosis of at least one bacterial infection/disease							3.18	3.08	3.29	1.60	1.54	1.67
Nursing home										3.59	3.37	3.82
Severe long-term care										2.06	1.83	2.32
Hospitalization										6.44	6.19	6.70

N = 105,216; OR, Odds ratio; CI, confidence interval; ASU, antibiotics for systemic use. Model 1: adjusted for age and sex. Model 2: adjusted for age, sex and Elixhauser comorbidity score. Model 3: adjusted for age, sex, Elixhauser comorbidity score and diagnosis of at least one bacterial infection/disease. Model 4: adjusted for age, sex, Elixhauser comorbidity score and diagnosis of at least one bacterial infection/disease and other control variables. Source: AOK data 2006–2018.

home residents only (results not shown; available on request).

Lag-time analysis

With one year lag-time, there was a negative association with a subsequent diagnosis of dementia for the total group of antibiotics (Fig. 2,

OR = 0.88, 95% CI: 0.85–0.91), tetracyclines (J01A) (Fig. 2, OR = 0.95, 95% CI: 0.91–0.99), beta-lactam antibacterials, penicillins (J01C) (Fig. 2, OR = 0.92, 95% CI: 0.88–0.95), other beta-lactam antibacterials (J01D) (Fig. 2, OR = 0.93, 95% CI: 0.89–0.97), macrolides, lincosamides, and streptogramins (J01F)

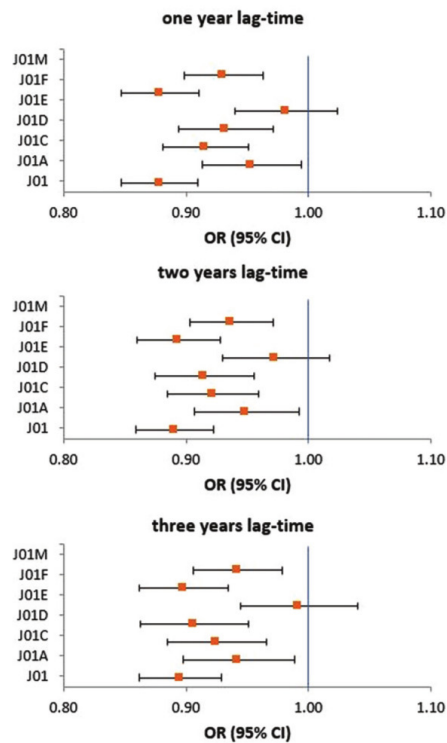


Fig. 2. Odds ratio and 95% confidence intervals of incident dementia one to three years after first prescription of antibiotics. OR, Odds ratio; CI, confidence interval; ASU, antibacterials for systemic use. All models were adjusted for age, sex, Elixhauser comorbidity score, diagnosis of at least one bacterial infection/disease, other control variables and the use of ASU of the other subgroups. Source: AOK data 2006–2018.

(Fig. 2, OR=0.88, 95% CI: 0.85–0.91), and quinolone antibacterials (J01M) (OR=0.93, 95% CI: 0.90–0.96). There was also a significant negative association for lag-times of two to three years for the total group of antibiotics (J01) (Fig. 2, OR=0.89, 95% CI: 0.86–0.93) and all subgroups, with exception of sulfonamides and trimethoprim (J01E) (Fig. 2, J01A: OR=0.94, 95% CI: 0.90–0.99; J01C: OR=0.92, 95% CI: 0.89–0.97; J01D: OR=0.91, 95% CI: 0.86–0.95; J01E: OR=0.99, 95% CI: 0.94–1.04; J01F: OR=0.90, 95% CI: 0.86–0.93; J01M: OR=0.94, 95% CI: 0.91–0.98).

Number of quarters with filled prescriptions

For a quarter with one filled antibiotic prescription, the OR was increased (Table 3, OR=1.02, 95% CI: 0.98–1.07). This positive association changed to a negative association with the number of quarters in which antibiotics were prescribed (Table 3, OR=0.80, 95% CI: 0.76–0.84). The subgroups beta-lactam antibiotics, penicillins (J01C), other beta-lactam antibiotics (J01D), and macrolides, lincosamides, and streptogramins (J01F), also revealed positive associations with a diagnosis of dementia (Supplementary Table 2). The results for sulfonamides and trimethoprim (J01E) are striking, with neither one quarter nor up to five quarters of prescriptions associated with a subsequent diagnosis of dementia (Supplementary Table 2).

DISCUSSION

For ASU, negative associations with dementia incidence were observed for the total antibiotic group (J01) and for the antibiotic subgroups except sulfonamides and trimethoprim (J01E). Differentiation by time since the first filled prescription did not change this association, which was present up to three years after the first filled prescription. For the total group of antibiotics (J01) and all subgroups of antibiotics, again with the exception of sulfonamides and trimethoprim (J01E), there were negative associations between increasing number of quarters with a filled prescription and a subsequent diagnosis of dementia.

Our results support the hypothesis that the sporadic use of ASU is associated with a decrease in dementia risk, once comorbidities and the presence of at least one bacterial infection or disease are controlled for, which was particularly evident for tetracyclines (J01A), beta-lactam antibacterials, penicillins (J01C), other beta-lactam antibacterials (J01D), macrolides, lincosamides, and streptogramins (J01F) and quinolone antibacterials (J01M). Our finding is in line with previous studies in patients with an existing cognitive impairment, which predominantly provided evidence of a positive effect of ASU on cognitive function. Administrations of the ASU rifampin and doxycycline, from the tetracycline drug class (J01A), significantly improved cognitive function after six months in patients with Alzheimer's disease and patients with mild to moderate dementia [40]. A follow-up study [8], however, could not con-

Table 3
Odds ratio of cumulative number of quarters by prescribed antibiotics for incident dementia

Cumulative number of quarters with ASU (J01)	Cases (N = 35,072)		Controls (N = 70,144)		OR ^a	[95% CI]	
	N	%	N	%			
0	9,495	27.07	21,148	30.15	Ref.		
1	7,372	21.02	14,195	20.24	1.02	0.98	1.07
2	5,298	15.11	10,008	14.27	0.94	0.89	0.99
3	3,642	10.38	7,142	10.18	0.87	0.82	0.92
4	2,536	7.23	4,910	7.00	0.88	0.82	0.94
5+	6,729	19.19	12,741	18.16	0.80	0.76	0.84

OR, Odds ratios; CI, confidence interval; ASU, antibiotics for systemic use. ^aadjusted for age, sex, Elixhauser comorbidity score, diagnosis of at least one bacterial infection/disease and other control variables. Source: AOK data 2006–2018.

firm these results, but found cognitive deterioration in ASU users.

Analyses with the broad-spectrum ASU amoxicillin, from the beta-lactam ASU drug class (J01C), comparing cognition in Alzheimer's disease patients suffering from bacterial infection by helicobacter pylori to the control groups without such infection and the control group with failed amoxicillin treatment showed significant differences in cognition between groups [41]. Cognitive and functional parameters improved in patients receiving successful antibacterial therapy, but not in the other groups. The effect may result from the control of pathogenic bacterial infection and the suppression of infection-associated systemic inflammatory processes. Systemic inflammation may harm brain function through several mechanisms including the sustained presence of pro-inflammatory mediators, the impairment of peripheral organ function, changes of brain perfusion or changes of the microbiome [42]. In keeping with this, harmful bacterial infections may also trigger dysbiosis of the gut microbiome, damage the gut barrier, and stimulate microorganisms to synthesize and release molecules that exert toxic effects in the brain [7, 41, 43]. Bacterial metabolites, e.g. short chain fatty acids, escaping the intestines can promote systemic disease and trigger neuroinflammatory responses in the brain [10]. Antibacterial therapy may eliminate pathogenic bacteria, thereby preventing or attenuating neuroinflammation [20–22, 43]. Immunological changes that occur in infection-induced delirium are similar to those that induce neuronal damage in Alzheimer's disease [18]. Infection-related inflammatory episodes accelerate the processes underlying cognitive dysfunction and decline, which may explain why infections accelerate cognitive decline in people with or without overt clinical symptoms and are thus associated with increased dementia risk, especially in the elderly, regardless of their severity [20, 21, 44].

Antibacterial therapy may also halt or prevent relapse of infection, which may explain the reduced effect in our time-delay analysis.

The effects of the different antibiotic treatments, with their various modes of action and antimicrobial spectra, and different distribution kinetics, point in the same direction. It might be possible that this result is due to the inflammatory process, and it is reasonable to assume that antibacterial therapies can in principle halt infection-induced inflammation, at least for a short period of time.

As mentioned above, rifampin and doxycycline, both belonging to the tetracycline drug class (J01A), have been found to cause cognitive deterioration [8]. One possible explanation may lie in the connection between the gut microbiome and the brain:

Alterations of the gut microbiome have been linked to cognitive aging and various neurological and neurodegenerative disorders. Thus, the microbiome can negatively impact on brain function and cause memory impairment. The gut microbiome and the brain affect each other in several ways through the so called gut-brain axis ultimately affecting human health [7, 17]. ASU act systemically, i.e., throughout the patient's body, and can disrupt the gut-brain axis. ASU enter the intestines and can change the microbiome there, thus disrupting the health-maintaining functioning of the gut [12–14, 45, 46]. Furthermore, the gut microbiome releases proinflammatory substances during an inflammatory process [43, 47–49]. The results of these antibacterial effects can be memory impairment and other cognitive dysfunctions [7]. Recent findings in a mouse model of tauopathy show an ApoE isoform and microbiota-dependent progression of neurodegeneration. Mice raised under germ-free conditions or shortly treated with antibiotics early in life to disrupt the gut microbiome exhibited reduced neurodegeneration [10, 50], which is in line with our findings.

Claims data and dementia registries are valuable for tracking dementia, but these record a dementia diagnosis with an average delay of about 5.5 years [51, 52]. Dementia is a gradual process that can begin years before the first clinical symptoms, so patients who are still recorded as ostensibly healthy in the data may already be suffering from the onset of cognitive change. Sporadic antibacterial use may attenuate or prevent the boosting effect of infection on cognitive change. While the acute episode could be prevented, cognitive decline cannot be completely halted and continues to progress insidiously. As a result, clinical symptoms only become apparent later and patients receive a delayed diagnosis. Our result³ that the risk of dementia declined with increasing number of quarters with prescriptions³ further supports this hypothesis. One quarter of prescriptions may not be sufficient to halt the boosting effect of infections.

The initial increased risk of ASU users compared to non-users can be fully explained by their comorbidity pattern and the presence of at least one bacterial infection or disease. This suggests that ASU are taken more often by comparatively morbid patients. Morbid patients with a higher number of comorbidities are generally sicker and at higher risk of being prescribed ASU. For example, patients with chronic diseases such as diabetes are more likely to have infections that need to be treated with ASU. However, these patients are also at a higher risk of developing dementia. Only after adjusting for comorbidity pattern and the presence of at least one bacterial infection or disease, the effect that dementia patients were less likely to be exposed to antibiotics than their control group becomes evident and supports our second hypothesis.

Limitations

Health claims data are only available for individuals using the medical system and they are intended to be used for billing rather than for an epidemiological analysis. Important risk factors associated with dementia are not included in these data, such as educational attainment, physical activity, and lifestyle factors such as tobacco or alcohol use [53]. We attempted to account for these factors by including comorbidities and nursing home status, which in turn are associated with a person's socioeconomic status. In addition, our data do not capture prescriptions from the inpatient sector. Our effects may therefore be underestimated, as people who only received a prescription in hospital are in the non-user group. All patients with a prescription for ASU have an

indication for that prescription, which itself may be associated with dementia. We have attempted to capture this by adjusting for diagnosis of at least one bacterial infection/disease. There are other factors known to be associated with the gut microbiome that are not captured by the health data used. Environmental factors, diet, and genetic conditions all play important roles in relation to a healthy gut microbiome. Supportive probiotic bacteria can be ingested through diet, which help provide the body with the necessary substances to prevent inflammation and associated diseases [7]. Another limitation is that the actual onset of dementia is unknown. However, we address this issue by excluding individuals with dementia in 2004 and 2005. We only have data on individuals aged 50 years and older, so we do not have information on exposure to administered ASU or comorbidities before the age of 50 and before the year 2004. In addition, the documented prescriptions for ASU do not indicate whether these were actually taken by patients, and the actual antibacterial use may be different. But in general, patients' adherence to ASU is considered high [54]. Our analysis of the effect of the cumulative number of ASU is limited by the small number of patients within the groups, which biases the results of the effect of prescription number and dementia risk.

The effects of the different antibiotic classes point in the same directions. Analyses with cohort data are needed to validate our results and examine individual antibiotics in more detail.

Conclusion

We believe that the association between dementia and sporadic antibiotic use in this case-control study provides valuable hypotheses. The reduction of dementia risk may be due to attenuation of inflammation, which in turn may reduce neurodegeneration. Our results are in line with previous findings that have emphasized the importance of preventing systemic inflammation in the elderly. Seemingly, the benefits of treating infections with ASU and the associated reduction in dementia risk must outweigh the risk of developing antibiotic resistance. Our analyses are intended to provide a first overview of how each class of ASU affects the risk of developing dementia. We hope that our results will stimulate further analyses of individual ASU groups or specific ASUs to unravel their potential benefit on cognition.

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CONFLICT OF INTEREST

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DATA AVAILABILITY

The data supporting the findings of this study are available on request from WIdO (webpage: <https://www.wido.de/>, mail: E-mail: wido@wido.bv.aok.de). The data are not publicly available due to privacy or ethical restrictions.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: <https://dx.doi.org/10.3233/JAD-221153>.

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Study II

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RESEARCH

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Dementia as a predictor of palliative care: Uncovering patient patterns based on German claims data

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Abstract

Background Palliative care aims to ensure a dignified and self-determined life for people facing the end of life. While palliative care is established for tumor diseases, it's notably absent from German medical guidelines for other progressive diseases with an unfavorable prognosis such as dementia. This study will identify predictors of palliative care use in older patients and explore how these predictors relate to the probability of palliative care.

Methods We used data from the largest German health insurance company of people over 50 years of age from the period 2014–2019. The analysis focused on the last year of life. Outcomes were outpatient and inpatient palliative care and predictors were demographics, comorbidities, therapeutic remedies and rehabilitation, care and medical interventions, medication and patient group. Combined logistic regression models and discrete conditional inference survival forests were used to predict the utilization of outpatient and inpatient palliative care. For evaluation we used concordance-index and calibration plots. We identified the most important predictors by using a permutation approach and the log-loss metric.

Results The study cohort for the analysis of inpatient palliative care comprised 43,896 patients, while the cohort for the analysis of outpatient palliative care included a total of 37,430 patients. The models had appropriate discriminatory power (inpatient palliative care: concordance-index = 0.737 (95%CI = 0.721–0.754); outpatient palliative care: concordance-index = 0.689; 95%CI = 0.675–0.704) and showed appropriate calibration. A diagnosis of dementia, like a diagnosis of cancer, is predictive of inpatient palliative care and outpatient palliative care. We observed a lower probability for inpatient and for outpatient palliative care for dementia patients compared to cancer patients.

Conclusions The findings highlight the need to focus palliative care on other patient groups besides cancer patients, such as dementia patients, and to facilitate access for all patients.

Keywords Dementia, Palliative care, End-of-life, Predictions, Machine learning

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Background

Hospice and palliative care in Germany include multi-professional care for people with incurable diseases and a limited life expectancy. The focus is on maintaining quality of life and ensuring a dignified death, as well as the alleviation of pain or other symptoms [1–3]. Palliative care can be provided on an outpatient or inpatient basis. Depending on need and cost, a distinction is made between general outpatient palliative care and specialized outpatient palliative care [3–5]. General outpatient palliative care includes palliative care that can be provided by primary care providers (primarily office-based primary care physicians, specialists, and outpatient care services) with basic palliative care training [6]. Care includes primary care visits and nursing services to manage the signs and symptoms of the disease [2, 4, 5, 7]. Specialist palliative home care services are available for complex cases, for patients at home, in nursing homes or long-term care facilities [3]. It includes specialized medical and nursing care, social interaction, and often even logotherapy and physiotherapy [8]. Patients with advanced disease, severe and difficult-to-control symptoms requiring hospitalization are eligible for inpatient palliative care.

Palliative care focus on a wide range of serious and progressive diseases and affected organs. This includes cancer as well as advanced heart, lung, kidney, neurological diseases and multimorbid geriatric patients [2, 9].

In Germany, medical guidelines (S3-guidelines [8]) recommend that patients with incurable cancer should have access to palliative care, regardless of disease stage or therapy [8]. In addition, patients should be offered palliative care after a diagnosis of incurable cancer, regardless of the targeted therapy. While the integration of palliative care for tumor diseases is increasingly established in oncology and general health care in cases of progressive disease and unfavorable prognosis, palliative care is surprisingly not mentioned in guidelines for other progressive diseases, such as dementia [10].

Demographic aging is leading to an increase in the total number of older people with limitations due to age and disease, who require temporary or permanent support or care. As a consequence, long-term care and palliative care are becoming increasingly important in the context of health care [11–13], as elderly morbid patients are predominantly cared for at home by family or self-funded professional care services [11]. With outpatient palliative care, the patient can receive additional support at home [3]. If the family cannot provide the care, care can be shifted to the inpatient care setting. The patient may receive outpatient specialist palliative care in a nursing home or can be admitted to an inpatient palliative care or hospice setting [3].

The rise in the elderly population will also lead to an increase in the number of people with dementia, as the

strongest risk factor for developing dementia is advancing age [14, 15]. Dementia is often not perceived as a life-limiting condition that requires palliative care, although it is an incurable, progressive process in which the patient gradually loses the ability to manage daily life and independence, often requires assistance and care, and with to a higher mortality rate [9]. Two-thirds of dementia patients in Germany currently receive informal care at home. As the number of dementia patients increases, the number of people in nursing homes will also rise. Although the symptom burden is similar to that of cancer patients, many dementia patients do not receive adequate and timely care [16].

Due to the discrepancy between care recommendations, and the associated increase in the care needs of patients at the end of life, we aim to investigate the utilization of end-of-life healthcare at in this paper. We aimed to identify predictors of palliative care utilization among older people and then examine the probability of palliative care.

We hypothesized that a cancer diagnosis is an important predictor of palliative care and increases its probability independently from in- or outpatient palliative care. In contrast, a dementia diagnosis is a less important predictor and reduces the probability of palliative care in any setting. Other important predictors are age and long-term care.

Methods

Data

We used longitudinal data from Germany's largest health insurance company, Allgemeine Ortskrankenkasse (AOK). The data sample was randomly drawn in 2014 from individuals aged 50 and older ($N=250,000$) and we followed them quarterly from the beginning of 2014 until the end of 2019. The data include demographic information on gender, year and month of birth and death (if applicable), place of residence, and whether or not the person lived in an institution. In addition, the sample contains information on all inpatient and outpatient diagnoses, coded according to the German modification of the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10). The data included filled prescriptions for medications coded according to the Anatomical Therapeutic Chemical Classification of Active Substances and Drugs code (ATC) and surgeries based on the German procedure classification, a modification of the International Classification of Procedures in Medicine (ICPM) (OPS, <https://www.dimdi.de/dynamic/en/classifications/ops/>, accessed: June 1, 2024). The data were anonymized claims data that did not require ethical review or patient consent.

Study design

To predict the probability of end-of-life palliative care, we selected individuals who died during the observation period and were observed for a one year prior to death (Supplementary Figure S1). In addition, skin cancer patients were excluded from the study group, as skin cancer can be detected and treated at an early stage through Germany's statutory cancer screening program. As a result, morbidity and mortality are significantly lower than for other types of cancer [17]. Our study cohort consisted of 37,430 patients. Since the data was unbalanced in terms of inpatient palliative care cases, the synthetic minority over-sampling technique (SMOTE) was used to increase the number of cases to address this issue [18, 19]. After up-sampling the observations, we had a study population of 43,896 for the inpatient palliative care analysis. For the outpatient palliative care analysis, we used the non-up-sampled study cohort of 37,430 patients.

We generated training, test, and validation data separately for outpatient and inpatient palliative care. To create training populations, we randomly selected 60% of each study cohort, stratified by palliative care (palliative care vs. no palliative care, see Sect. 2.3 for more details), time to diagnosis and patient groups (see Sect. 2.4 for more details). The remaining subjects each study cohort were equally divided into validation and test groups. We trained the models on training datasets and used the validation datasets to find the optimal parameter values. Finally, we fit the models with optimal parameter values to the test data.

Outcomes

The outcome for outpatient palliative care (OPC) was a binary variable and included general outpatient palliative care and specialized palliative care, as well as palliative care (PC) in primary care. The outcome for inpatient palliative care (IPC) was also a binary outcome. The precise definitions of both are provided in Supplementary Table S1. Both outcomes were defined according to ICD-10, Einheitlicher Bewertungsmaßstab (EBM) and Operationen- und Prozedurenschlüssel (OPS). EBM is the uniform valuation scale for services provided by registered physicians and registered psychotherapists in Germany. It is a social security list in the German health care system according to which outpatient and physician services are covered by health insurance. OPS is an official classification for the systematic recording and coding of all operations, procedures and general medical measures.

Exposure

We categorized patient status into six subgroups: dementia patients (ICD-10 codes: F00-F03, F05.1, G30, G31.0), cancer patients (ICD-10 codes: C00-C41, C45-C97), patients with a diagnosis of dementia and cancer, and

patients without a dementia diagnosis and without a cancer diagnosis (in the following referred as non-dementia & non-cancer). The group with a diagnosis of cancer and diagnosis of dementia was further divided into three subgroups: patients who received a diagnosis of dementia and a diagnosis of cancer within 12 months (referred as cancer & dementia), patients who received a diagnosis of dementia first and a diagnosis of cancer at least 12 months apart (referred as dementia & subsequent cancer), patients who received a diagnosis of cancer first and a diagnosis of dementia at least 12 months apart (referred as cancer & subsequent dementia). All were included as time-dependent binary "ever" variables with a value of 1 starting from the first occurrence of a disease and zero otherwise. Patient status may change over time. For example, a patient may be in the non-dementia & non-cancer group at baseline and receive a diagnosis of dementia during the observation period. At this point, the patient moves to the patient status dementia patients and the old patient status variable (non-dementia & non-cancer) is reset to zero and the new patient status variable (dementia patients) is set to one. Thus, only one patient status group applies to a person at a time.

Predictors

We included the following predictors and categorized them into five different groups. **Therapeutic remedies and rehabilitation:** physiotherapy, occupational therapy, speech therapy, other therapies (excluding physiotherapy, occupational therapy, and speech therapy), general practitioner (GP) visits, neurologist visits, doctors' visits (without GP and neurologist) and rehabilitation. Further information can be found in Supplementary Table S2. **Medical interventions and major medications:** chemotherapy, nuclear therapy, radiotherapy, cancer and dementia drugs. **Comorbidities** defined by the Elixhauser index [20]: hypertension, diabetes, chronic pulmonary disease, congestive heart failure, depression, cardiac arrhythmias, fluid and electrolyte disorders, rheumatoid arthritis/collagen vascular disease, renal failure, valvular disease, peripheral vascular disease, coagulopathy, pulmonary circulatory disorders, liver disease, obesity, paralysis, deficiency anemia, hypothyroidism, drug abuse, peptic ulcer disease, weight loss, AIDS/HIV, blood loss anemia, alcohol abuse and neurological disorders without dementia. All descriptions of the comorbidities can be found in Supplementary Table S3. **Category care interventions** included information on whether patients lived in a nursing home and on the presence or absence of severe care dependency, where severe care dependency was defined as care level 3 (until the end of 2016) or care level 5 (from 2017), IPC and OPC (according to model) and information on the number of hospital days. Further details on long-term care including

definition on care levels are available in Supplementary Method S1. We also included **demographics** such as age at baseline and sex.

All predictors except age, sex, different physician visits, and number of hospital days, were included as time-dependent binary “ever” variables with a value of 1 starting from the first occurrence of a given code and zero otherwise.

Statistical analysis

The longitudinal information of the patients was analyzed using discrete time-to-event analysis with time since start of observation in quarters as analysis time. Since all observations started one year before death the maximum number of observed quarters was four. To predict the probability of PC, we used a combination of a logistic regression model (glm) and discrete conditional inference survival forests (cforests) [21]. Glm and cforest predictions were predicted individually and then averaged without weighting. The input data for these models consisted of one row per quarter and patient with information on the utilization of IPC, OPC and time-dependent predictors (as described in Sect. 2.5). All calculations were done in R version 4.1.3 (2022-03-10). For cforest, we used the partykit package (version 1.2.16) [22] to perform separate models for OPC and IPC. In addition, we calculated separately logistic regression models and a conditional inference survival forests for both outcomes in a sensitivity analysis.

To indicate whether the predicted features increase or decrease the probability of PC, we calculated odds ratios (OR) for each outcome using the 20 most important features.

Model evaluation

We calculated the concordance index (c-index) to assess discriminatory power using the discSurv package (version 2.0.0) [23], 95% confidence intervals (95% CI) were calculated using 1000 bootstrap replications from the test data. In addition, we examined calibration plots (to graphically assess model calibration) and calculated a logistic recalibration intercept and slope to assess whether predicted risks were systematically over- or underestimated. To maximize model performance, we used the validation data to adjust the “mtry” parameter (the number of input variables randomly samples at each node available for splitting). Using a permutation approach and the log-loss metric, we identified the key features for prediction.

Results

First, we examined whether our study sample reflected the use of PC at the end of life in Germany. For this purpose, we analyzed the development of the utilization

rates for OPC and IPC (percentage of deceased insured persons with OPC or IPC out of all deceased insured persons in a given year). The use of OPC increased from 25.5 to 28.8% from 2015 to 2019. IPC use increased from 7.7 to 8.5%. The results of the utilization rates for OPC and IPC can be found in Supplement Figure S2.

Study cohort

Study population for inpatient palliative care at baseline

Our study cohort consisted of 43,896 patients, of whom 20,015 (45.60%) were male and 23,881 (54.40%) female. At baseline the mean age was 78.62 years. 558 patients (1.27%) received IPC and about 20% of the patients were already living in a nursing home at baseline. (Table 1). A cancer diagnosis was documented for 21.72% of the study participants; 24.84% had a dementia diagnosis, 47.71% had neither dementia nor a cancer diagnosis. About 5% had a combination of dementia and cancer diagnosis. The most common comorbidities in the study group were diabetes (43.48%), congestive heart failure (42.33%), cardiac arrhythmias (39.54%) and renal diseases (35.71%). Dementia-related medications were prescribed to more than 40% of patients (Table 1). The average observation period was 2.94 quarters (one quarter minimum, four quarters maximum).

During the observation period, the distribution of patients between groups changed. At the beginning of the observation period, most patients were still non-dementia & non-cancer patients, but by the quarter of death, the largest group were the dementia patients with 32.79%. Non-dementia & non-cancer patients were the second largest group with 31.28%, followed by the cancer patients (24.77%). The proportion of the patients group cancer & dementia increased to 6.05%, the group dementia & subsequent cancer increased to 2.17%, and the group cancer & subsequent dementia increased to 2.95%. In subsequent quarters, the proportion of patients with an IPC prescription increased to a proportion of 11.89%. All results can be found in supplement Table S4.

Inpatient palliative care patients at prescription

At time of IPC prescription ($N=9,699$), more than half (57.26%) were diagnosed with cancer (Table 1). Non-dementia & non-cancer patients were the second largest group, accounting for 18.79% of all IPC patients. Patients were often affected by disturbances in fluid and electrolyte balance (64.14%), peripheral vascular disorders (46.19%), congestive heart failure (44.95%), and peripheral vascular disorders (44.36%). More than a third of patients (34.43%) were already receiving OPC.

Study population for outpatient palliative care at baseline

The dataset included a total of 37,430 patients. Of these, 48.77% had no dementia & no cancer diagnosis, 27.13%

Table 1 Characteristics of the study population at baseline and the time of prescription of IPC

	Study population for IPC at baseline (N = 43,869*)		IPC patients at prescription (N = 9,699)	
	N	%	N	%
Outcome				
Inpatient palliative care	558	1.27	9,699	100.00
Patient group				
Cancer	9,534	21.72	5,554	57.26
Dementia	10,902	24.84	1,297	13.37
Non-dementia & non-cancer	20,944	47.71	1,822	18.79
Cancer & dementia	1,752	3.99	578	5.96
Dementia & subsequent cancer	267	0.61	202	2.08
Cancer & subsequent dementia	497	1.13	246	2.54
Demographics				
Time since observation (mean)	4		3.93	
Age at baseline (mean)	78.62		74.83	
Men	20,015	45.60	4,697	48.43
Comorbidities				
Disturbances in fluid and electrolyte balance	14,872	33.88	6,221	64.14
Weight loss	4,894	11.15	3,144	32.42
Congestive heart failure	18,581	42.33	4,360	44.95
Peripheral vascular disorders	14,646	33.37	4,480	46.19
Cardiac arrhythmias	17,355	39.54	4,302	44.36
Renal disease	15,674	35.71	4,133	42.61
Depression	13,756	31.34	3,906	40.27
Diabetes	19,088	43.48	4,229	43.6
Therapeutic remedies and rehabilitation				
Doctor's visits (without GP and neurologist) (mean)	3.72		4.98	
Care interventions				
Outpatient palliative care	2,161	4.92	3,339	34.43
Nursing home	8,537	19.45	1,753	18.07
Medical interventions and major medications				
Chemotherapy	1,927	4.39	1,579	16.28
Dementia drugs	18,504	42.15	4,281	44.14
Radiotherapy	525	1.2	813	8.38

We report only the 20 most influential predictors in terms of variable importance (Fig. 1). IPC: inpatient palliative care, * data up sampled. Data: AOK data from 2014–2019

had a dementia diagnosis and 18.14% had a cancer diagnosis. Around 6% of patients had a cancer and dementia diagnosis (Table 2). The mean age at baseline was 79.28 years. The most common comorbidities with a frequency of over 30% were disturbances in fluid and electrolyte balance, depression and renal disease (Table 2). About 21% of all patients live in a nursing home and 8% receive long-term care. The average observation period was 2.94 quarters (one quarter minimum, four quarters maximum).

The distribution of patients among the groups changed during the observation period. The proportion of non-dementia & non-cancer patients decreased over the observation period from 48.77 to 34.87%, while the proportion of patients in all other patient groups increased. At the end of the observation period, 33.99% of the patients had a dementia diagnosis and 20.93% had a cancer diagnosis. 5.57% of the patients were cancer &

dementia patients, and 1.85% of the patients were dementia & subsequent cancer patients. The proportion of cancer & subsequent dementia patients was 2.79%. At baseline, 4.31% of patients ($n=1,612$) were already receiving OPC prescriptions. In subsequent quarters, the proportion of patients with a prescription varied. Only shortly before death the proportion of patients increased to 15.36% (quarter of death). All results can be found in supplement Table S5.

Outpatient palliative care patients at prescription

OPC patients ($N=9,992$) were predominantly cancer patients (41.57%), followed by dementia patients (30.77%) (Table 2). Women were more likely to receive OPC (58.13%) and the most common comorbidities were disturbances in fluid and electrolyte balance (68.04%), renal

Table 2 Characteristics of the study population at baseline and the time of prescription of OPC

	Study population for OPC at baseline (N = 37,430)		OPC patients at prescription (N = 9,992)	
	N	%	N	%
Outcome				
Outpatient palliative care	1,612	4.31	9,992	100.00
Patient group				
Cancer	6,791	18.14	4,154	41.57
Dementia	10,154	27.13	3,075	30.77
Non-dementia & non-cancer	18,256	48.77	1,288	12.89
Cancer & dementia	1,559	4.17	833	8.34
Dementia & subsequent cancer	237	0.63	333	3.33
Cancer & subsequent dementia	433	1.16	309	3.09
Demographics				
Time since observation (mean)	4		3.81	
Age at baseline (mean)	79.28		79.46	
Men	16,903	45.16	4,184	41.87
Comorbidities				
Weight loss	4,000	10.69	3,165	31.68
Disturbances in fluid and electrolyte balance	12,753	34.07	6,799	68.04
Depression	11,683	31.21	4,293	42.96
Paralysis	4,065	10.86	1,817	18.18
Renal disease	13,679	36.55	4,947	49.51
Therapeutic remedies and rehabilitation				
Doctor's visits (without GP and neurologist) (mean)	3.68		5	
Physiotherapy	5,314	14.2	1,890	18.92
Rehabilitation	360	0.96	275	2.75
Care interventions				
Long-term care	3,001	8.02	2,349	23.51
Nursing home	8,000	21.37	3,852	38.55
Inpatient palliative care	186	0.5	1,118	11.19
Medical interventions and major medications				
Chemotherapy	1,169	3.12	1,047	10.48
Radiotherapy	330	0.88	362	3.62

We report only the 20 most influential predictors in terms of variable importance (Fig. 2). OPC: outpatient palliative care. Data: AOK data from 2014–2019

disease (49.51%), and depression (42.96%). In addition, 11.19% of patients had previously received IPC.

Model evaluation

First, we used both a glm and a cforest to predict IPC as well as OPC. The cforest had a higher discriminatory power than the glm model for the prediction of IPC. However, the calibration of the cforest was worse than that of the glm model. All results are shown in Supplementary Table S6 and Figure S3. Therefore, we used a combined model of both approaches. The c-index was 0.737 (95% CI=0.721–0.754), and the calibration was acceptable with an intercept of -0.023 (95% CI = -0.030 - -0.016) and a slope of 1.418 (95% CI=1.332–1.504) (Fig. 3).

The discriminative power of glm and cforest for OPC was comparable. The glm model tended to slightly overestimate the predicted values, while the cforest had the opposite effect and tended to underestimate the

predictions. All results are shown in Supplementary Table S6 and Figure S3. Again, we decided to combine both models to predict OPC. The c-index was 0.689 (95% CI = [0.675–0.704]), and the calibration plot showed that the combined model was better calibrated than the individual models, with intercept close to 0 and slope close to 1 (intercept: -0.006; 95% CI = -0.010 - -0.003; slope: 1.122; 95% CI= 1.083–1.161) (Fig. 3).

Most important variables

Inpatient palliative care

The most important variable was the time since observation (Fig. 1). The second and third most important variables were cancer diagnosis and age at baseline. In addition to cancer diagnoses, non-dementia & non-cancer, and dementia diagnoses were among the top 20 predictors (3/6). Eight diseases from the comorbidities (disturbances in fluid and electrolyte balance, weight loss, congestive heart failure, peripheral vascular disorders,

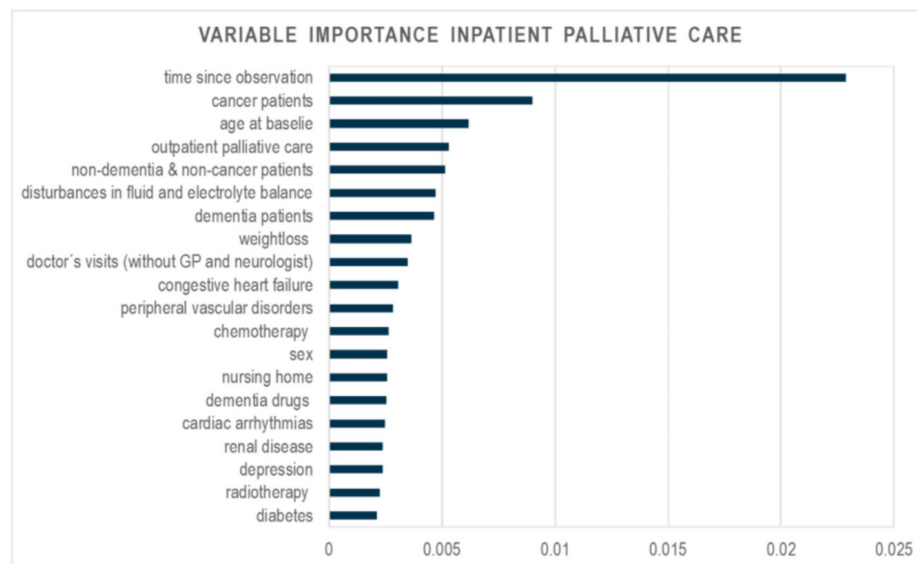


Fig. 1 Variable importance for the model of inpatient palliative care. AOK data 2014–2019

cardiac arrhythmias, renal disease, depression and diabetes) (8/28) and one therapeutic remedy and rehabilitation (number of doctor's visits) (1/8) were among the most predictive factors. Three medical interventions and major medications (chemotherapy, dementia medications, radiotherapy) (3/5), and two care interventions (OPC and nursing home) (2/5) were also among the top 20 predictors.

The probability of prescribing IPC was primarily increased by characteristics of comorbidities, medical interventions and major medications (Supplement Figure S4). Patients who receive chemotherapy (OR=1.51; 95% CI=1.41–1.61), radiation therapy (OR=1.10; 95% CI=1.05–1.15), or dementia drugs (OR=2.95; 95% CI=2.69–3.24) had an increased probability of IPC compared to patients who did not receive any of these medical interventions or major medications (Table 3). With each quarter of observation, the probability of IPC increased. Women and patients who had already received OPC had a significantly increased probability of IPC (women: OR=1.16, 95% CI=1.11–1.22; OPC: OR=1.65 95% CI=1.56–1.73).

All patient groups had a significantly lower probability of receiving IPC compared to cancer patients (dementia: OR=0.28, 95% CI=0.26–0.30; non-dementia & non-cancer: OR=0.30, 95% CI 0.20–0.32; cancer & dementia: OR=0.61, 95% CI=0.56–0.67; dementia & subsequent

cancer: OR=0.70, 95% CI=0.60–0.82; cancer & subsequent dementia: OR=0.58, 95% CI=0.51–0.67).

Outpatient palliative care

The most important predictor was time since observation (Fig. 2). This was followed by non-dementia & non-cancer diagnosis and cancer diagnosis. In addition to these diagnosis dementia, cancer & dementia were predictive for OPC (4/6). The comorbidities weight loss, disturbances in fluid and electrolyte balance, depression, paralysis and renal disease (5/28) were predictive for OPC. In addition to time since observation, the demographic factors of age at baseline and sex were important predictors of OPC (3/3), as well as long-term care, IPC and nursing home from care interventions (3/5), doctors' visits (without GP and neurologist), physiotherapy and rehabilitation from therapeutic remedies and rehabilitation (3/8), and chemotherapy and radiotherapy from medical interventions and major medications (2/5).

The probability of an OPC prescription was mainly influenced by the comorbidity structure of the patients, as well as therapeutic remedies, rehabilitation and care interventions (Supplement Figure S5). The OPC probability increased significantly with the use of physiotherapy (OR=1.09; 95% CI=1.03–1.15), rehabilitation (OR=1.58; 95% CI=1.38–1.82), chemotherapy (OR=2.05; 95% CI=1.89–2.23) and radiotherapy (OR=1.57; 95%

Table 3 Odds ratios from logistic regression with inpatient palliative care as the outcome

Inpatient palliative care	Odds Ratio	P> z	[95% Conf. Interval]	
Demographics				
Time since observation	1.71	<0.001	1.67	1.74
Age at baseline	0.99	<0.001	0.98	0.99
Sex				
Male	Ref			
Female	1.16	<0.001	1.11	1.22
Patients group				
Cancer patients	Ref.			
Dementia patients	0.28	<0.001	0.26	0.30
Non-dementia & non-cancer patients	0.30	<0.001	0.29	0.32
Cancer & dementia patients	0.61	<0.001	0.56	0.67
Dementia & subsequent cancer patients	0.70	<0.001	0.60	0.82
Cancer & subsequent dementia patients	0.58	<0.001	0.51	0.67
Comorbidities				
Disturbances in fluid and electrolyte balance	1.35	<0.001	1.29	1.42
Weight loss	1.35	<0.001	1.28	1.42
Congestive heart failure	0.85	<0.001	0.81	0.90
Peripheral vascular disorders	1.13	<0.001	1.08	1.18
Cardiac arrhythmias	0.93	0.005	0.89	0.98
Renal disease	0.97	0.209	0.92	1.02
Depression	1.10	<0.001	1.05	1.15
Diabetes	0.99	0.538	0.94	1.03
Therapeutic remedies and rehabilitation				
Doctor's visits (without GP and neurologist)	1.01	<0.001	1.01	1.01
Care interventions				
Outpatient palliative care	1.65	<0.001	1.56	1.73
Nursing home	0.73	<0.001	0.68	0.77
Medical interventions and major medications				
Chemotherapy	1.51	<0.001	1.41	1.61
Dementia drugs	1.10	<0.001	1.05	1.15
Radiotherapy	2.95	<0.001	2.69	3.24

Controlled for the top 20 predictors. AOK data 2014–2019

CI=1.38–1.80) (Table 4). Patients with existing care intervention also had an increased probability of OPC compared to patients without these care (long-term care: OR=1.93, 95% CI=1.83–2.05; nursing home: OR=1.49, 95% CI=1.41–1.57; IPC: OR=1.97, 95% CI=1.82–2.13).

The probability of OPC was lower in all groups (except those with dementia & subsequent cancer diagnosis) compared to those cancer diagnosed (dementia: OR=0.33; 95% CI=0.31–0.36; non-dementia & non-cancer: OR=0.18; 95% CI=0.17–0.19; cancer & dementia: OR=0.64; 95% CI=0.59–0.70; and cancer & subsequent dementia: OR=0.54; 95% CI=0.48–0.62).

Discussion

A diagnosis of dementia was a significant predictor of the use or non-use of PC, along with cancer. Patients with dementia had a significantly lower probability of both IPC and OPC compared to patients with cancer. They even had the lowest probability of receiving IPC. This is in line with existing studies on the patient situation in

PC, where cancer patients still represent the largest proportion of patients [24, 25]. Furthermore, our data reflect the use of PC at the end of life in Germany and confirm the findings of Ditscheid et al. [26].

Inpatient palliative care

Time since observation were the most important factors predicting IPC. Even though early integration of PC has been proven to be beneficial for patients with progressive life-limiting diseases [27], in practice, the involvement of PC often occurs near death [28]. Dementia diagnoses are among the ten most important predictors of IPC. We had expected that patients with a dementia diagnosis would have a lower probability of IPC than patients with a cancer diagnosis. Our analyses validated this hypothesis, as all other patient groups in our study exhibited a significantly lower probability of IPC than cancer patients. In particular, the patient group without a combined cancer diagnosis (non-dementia & non-cancer as well as dementia) had a significantly lower probability. Surprisingly, the

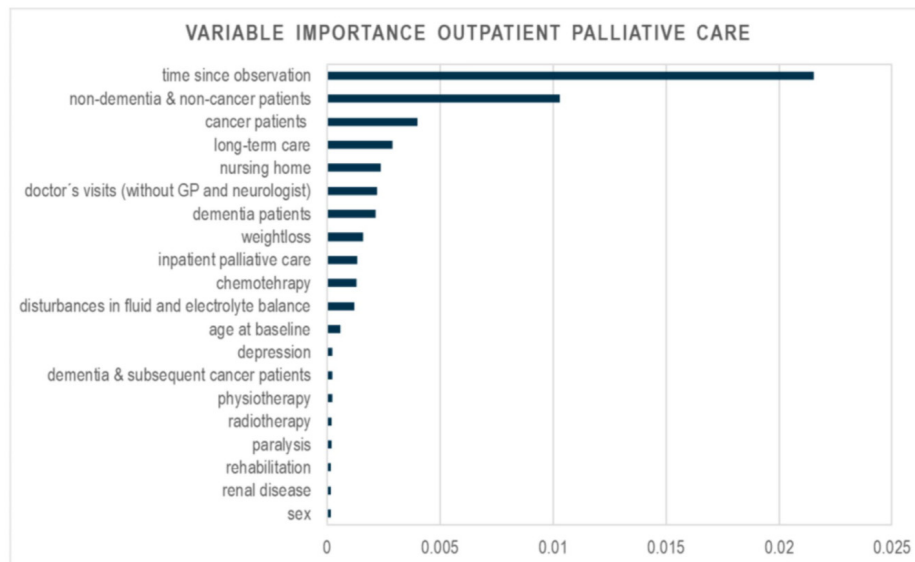


Fig. 2 Variable importance for the model of outpatient palliative care. AOK data 2014–2019

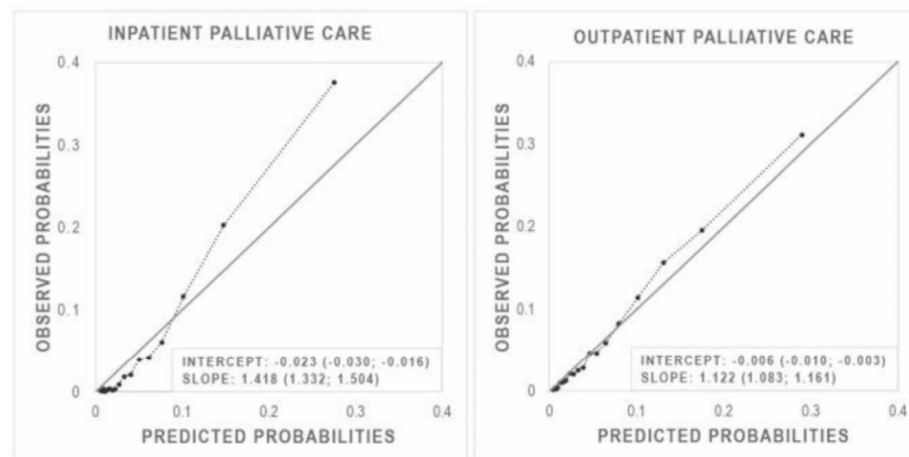


Fig. 3 Calibration plots. Intercepts and slopes were calculated using logistic recalibration (95% confidence intervals in parentheses)

patient groups with a combined cancer diagnosis (cancer & dementia, dementia & subsequent cancer and cancer & subsequent dementia) also showed a significantly lower probability.

This may be explained by the fact that most old people with dementia live in private households as well as in nursing homes and residential care facilities [29]. Instead of using IPC facilities, they and their families

Table 4 Odds ratios from logistic regression without patient palliative care as the outcome

Outpatient palliative care	Odds Ratio	P > z	[95% Conf. Interval]	
Demographics				
Time since observation	1.46	<0.001	1.44	1.49
Age at baseline	1.00	0.002	1.00	1.01
Sex				
Male	Ref.			
Female	1.12	<0.001	1.07	1.17
Patient groups				
Cancer patients	Ref.			
Dementia patients	0.33	<0.001	0.31	0.36
Non-dementia & non-cancer patients	0.18	<0.001	0.17	0.19
Cancer & dementia patients	0.64	<0.001	0.59	0.70
Dementia & subsequent cancer patients	1.00	0.954	0.88	1.15
Cancer & subsequent dementia patients	0.54	<0.001	0.48	0.62
Comorbidities				
Weight loss	1.57	<0.001	1.50	1.65
Disturbances in fluid and electrolyte balance	1.39	<0.001	1.33	1.46
Depression	1.17	<0.001	1.11	1.22
Paralysis	1.07	0.025	1.01	1.13
Renal disease	1.00	0.856	0.96	1.05
Therapeutic remedies and rehabilitation				
Doctor's visits (without GP and neurologist)	1.03	<0.001	1.03	1.03
Physiotherapy	1.09	0.002	1.03	1.15
Rehabilitation	1.58	<0.001	1.38	1.82
Care interventions				
Long-term care	1.93	<0.001	1.83	2.05
Nursing home	1.49	<0.001	1.41	1.57
Inpatient palliative care	1.97	<0.001	1.82	2.13
Medical interventions and major medications				
Chemotherapy	2.05	<0.001	1.89	2.23
Radiotherapy	1.57	<0.001	1.38	1.80

Controlled for the top 20 predictors. AOK data 2014–2019

and caregivers may prefer OPC [30], which allows them to stay in their familiar home surroundings until death. Dementia patients who received IPC are more likely to show signs of advanced dementia [31], characterized by symptoms such as disorientation, helplessness, and inability to perform activities of daily living [32], beyond the point at which patients could be cared for at home as outpatients. Another barrier to IPC may be accessibility. Due to a lack of guidelines and indications for PC for patients with dementia, many patients have difficulty accessing care [10].

Patients who had already received OPC had an increased probability of IPC. These patients represent an already morbid patient population with the prospect of premature death or need for assistance with daily living and self-care [2, 4]. In cases of severe acute symptoms that cannot be adequately controlled in an outpatient setting, the patient may be transferred to an inpatient setting where PC physicians and nurses use a variety of medical and nursing interventions to re-stabilize the patient and, if possible, even discharge the patient home [7].

Outpatient palliative care

We hypothesized that a cancer diagnosis would be an important predictor of PC and a dementia diagnosis would be a less important predictor. Both diagnosis groups rank among the top predictors, but as expected, the probability of OPC was lower in dementia patients compared to cancer patients. Specialized OPC offers the possibility of receive high-quality OPC not only at home but also in institutions. In Germany, most people with early stages of dementia remain at home and are cared for by family members [31, 33], and almost half of patients with dementia are receive care at home until death [34]. It is difficult to determine the optimal point in time when PC for dementia patients should be initiated [9, 35, 36]. During the final stage of life, people with advanced dementia may encounter significant physical and psychological symptoms. Various outpatient medical and nursing interventions can alleviate symptoms and enhance wellbeing. Physicians and outpatient care services with basic training in PC provide appropriate end-of-life care to dementia patients [34]; however, such care

is not yet implemented regularly for people diagnosed with dementia, so many patients struggle to receive appropriate end-of-life care [10].

The probability of OPC is driven by the comorbidity structure, therapeutic remedies and rehabilitation as well as care interventions of the patients. Patients who have previously received long-term care, lived in a nursing home, or received care in an IPC facility have a high probability of being dependent on assistance. It is not surprising, therefore, that these patients had an increased probability of needing OPC compared to those without prior care experience. When basic PC interventions as part of primary care are no longer sufficient to alleviate symptoms specialist OPC can provide additional support for both patients and their families and caregivers [3]. Patients receiving IPC are more likely to require OPC services although most patients die in hospital [37]. This may be related to the fact that patients who have been discharged from IPC and who may not have died during IPC are at a higher risk of requiring OPC. The fundamental objective of IPC in Germany is to alleviate the symptoms and therapeutic interventions associated with the disease, thereby stabilizing the patient's condition and facilitating discharge home or transition to another care facility [37]. These patients continue to receive OPC after being discharged from IPC.

Lack of communication and knowledge deficits about PC as well as the stigma of PC as an intervention for the imminently dying remain as additional barriers that may impede access to palliative care [38].

Our finding that women are at higher more likely to receive PC is well known [39, 40] and may be due to a variety of influences, including gender roles, stress, lifestyle, and preventive health measures [40]. Women also have a higher risk of lacking a support system. Statistically, women live longer than men [41], so often the sick husband can be cared for by the wife, but if she becomes ill later, the husband has often already died and she is dependent on other support systems.

Strength and limitations

The study benefits from large, comprehensive data collected from the inpatient and outpatient sectors including nursing homes in Germany, which increases the validity of the study conducted. The standardized survey reduces problems such as selection and recall bias. However, the data are primarily used for billing purposes, which limits the generalizability of the results, especially for individuals who did not visit a physician. Additionally, the AOK has a higher percentage of individuals with a low socioeconomic status compared to other statutory health insurers and even in comparison to private health insurers in Germany [42]. While these disparities could potentially affect both morbidity and the utilization of

healthcare services, they can be partially attributed to the differing age distribution within the AOK population, which is older than the German population. When considering patients of the same age, the difference in the social structure of the AOK population is more pronounced in younger age groups than in older ones [43, 44]. Information on medical prescriptions is limited to the filling of the prescription, without information on the actual intake of the medication.

In addition, there were initial problems in tuning the models. The cross-entropy based log-loss metric was employed to measure prediction quality. Tuning regarding c-index resulted in loss of calibration. Therefore, a combined model of glm model and cforest was selected as a compromise between c-index and calibration model coefficients. It is worth noting that the fitted model is only marginally better than the untuned model in terms of the c-index and the calibration model coefficients. Possible data-related issues should be considered. Our dataset comprised a limited number of cases of IPC, thus we conducted an up-sampling beforehand to artificially increase the sample.

To incorporate time-variable switching conditions and integrates IPC and OPC could represent a promising future advancement. However, it is imperative to consider that patients in Germany have the option of transitioning between IPC and OPC. The development of models that take this switching into account is only possible on the condition that the order of prescriptions is clearly recognizable in the data. The nature of our data collection process, which is conducted on a quarterly basis, precludes the identification of the sequence in which prescriptions are made. Further research can consider the integration of IPC and OPC, including time-varying switching conditions.

The provision of PC in Germany is influenced by both socioeconomic and medical factors [45], but socioeconomic variables were not included in our data. The decision to provide support depends on the person in need of care, where they live, and their care needs and the caregiver [11]. In 2021, 84% of Germans in need of long-term care were receiving care at home from informal caregivers and professional care services [33]. Providing care at home for relatives results in financial losses for the family caregiver since they have to reduce their working hours that ensure income if they are below retirement age [46].

Socioeconomically disadvantaged individuals demonstrate an increased need for medical care compared to the general population [47]. Access to PC services depends on physician referrals, as referral patterns for PC are not standardized, depend on many patient and provider characteristics, and are not necessarily based on actual need [47]. Individuals with low social security often have limited access to health care services [47].

Further analyses of PC with other data are advised to adequately address socioeconomic factors in addition to medical factors.

Conclusions

Our analyses suggest that a diagnosis of dementia, like a diagnosis of cancer, is predictive of both IPC and OPC, even though dementia patients appear to have a much lower chance to access palliative care. It seems that dementia patients are less likely to receive both IPC and OPC. Particular attention should be paid to dementia patients with pre-existing comorbidities and those who are already in contact with the care system (either through nursing and medical interventions or through therapeutic and rehabilitative interventions). Patients with pre-existing care needs, such as long-term care, nursing home residents and rehabilitants, appear to be more likely to receive PC. These patients may have already exhausted all care interventions outside of PC, so that symptom control and care are still possible only in the inpatient setting. Another group with a comparatively high probability of PC are older women, which may indicate a lack of informal social support in older age. Our findings underline the need to focus PC on other patient groups besides cancer patients, such as dementia patients, and to facilitate access for all patients.

Abbreviations

AOK	Allgemeine Ortskrankenkasse
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th revision
ATC	Anatomical Therapeutic Chemical Classification of Active Substances and Drugs code
ICPM	International Classification of Procedures in Medicine
SMOTE	Synthetic minority over-sampling technique
PC	Palliative care
OPC	Outpatient palliative care
IPC	Inpatient palliative care
EBM	Einheitlicher Bewertungsmaßstab
OPS	Operationen- und Prozedurenschlüssel
GP	General practitioner
GLM	Logistic regression model
Cforest	Discrete conditional inference survival forests
C-index	Concordance index
95% CI	95% confidence intervals
OR	Odds ratio

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12904-025-01672-y>.

Supplementary Material 1

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Author contributions

ER and GD conceptualized the study. Data were analyzed by ER, MS, TW, CR and ER contributed to the methodology. Project management and resources were provided by GD. The project was supervised by GD. The study was validated by LK, CR, GD, MS and TW. The original draft of the manuscript and the visualisation of the results were prepared by ER. All authors were involved in draft revisions and approving the final draft for submission.

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Data availability

The data that support the findings of this study are available from Scientific Institute of the AOK (WiDO) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the Scientific Institute of the AOK (WiDO) upon reasonable request and with permission.

Declarations

Ethics approval and consent to participate

The Ethics Committee of the University Medical Center Rostock has stated no ethical concerns to this study. All analyses of this study are based on anonymized German administrative health claims data which never identify patients directly. As individuals are anonymous, the results presented here do not in any way affect the persons whose records were used. This study complies with the tenets of the Declaration of Helsinki, and the use of routinely collected data for scientific purposes is regulated by federal law, so informed consent to participate was not required.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Study III

Exploring the Impact of Social Networks and Cognitive Function on All-Cause Mortality in Older Adults: Insights from the German National Cohort (NAKO)

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ABSTRACT

Both social network integration and cognitive performance contribute to adult survival. However, the combined effect on mortality remains unclear.

We used data from the baseline examination (2014-2019) of the German National Cohort study, aged 60 years and older. Vital status was assessed by the end of 2023. Cognition was measured using semantic memory (SM) and executive function (EF); and social integration by the Social Network Index (SNI). Hazard ratios (HR) and 95% confidence intervals (CI) were calculated using Cox proportional hazards models to estimate the association between cognition, SNI and mortality. Interaction terms were calculated between SNI and SM and between SNI and EF.

A total of 55,178 participants were analyzed, of whom 2,524 died during the observation period. Mortality risk was significantly lower among individuals with moderate and high EF compared to those with low EF. We found a similar pattern for SM, although none of the results were significant. Individuals moderately integrated into social networks showed reduced mortality risk compared to those with SNI level I.

Adding interaction terms between SNI and cognitive domains revealed U-shaped patterns of mortality risk, with the exception of high EF. Specifically, when combined with SNI level III, mortality risk was significantly lower than the individual risks (SM_low: HR=0.46, 95%CI=[0.33-0.65]; SM_moderate: HR=0.72, 95%CI=[0.59-0.88]; SM_high: HR=0.56, 95%CI=[0.37-0.86]; EF_low: HR=0.54, 95%CI=[0.38-0.75]; EF_moderate: HR=0.65, 95%CI=[0.54-0.79]). These findings emphasize the importance of social network integration in reducing mortality risk among older adults. Importantly, even a moderate level of social integration appears sufficient to confer a survival benefit.

Keywords: Mortality, cognition, social network, social integration, older adults

Introduction

A total of 1.03 million people died in Germany in 2023, a decrease of 3.6% compared to the previous year [1]. The number of deaths fell for the first time since 2019, and more than half of all deaths were among people aged 85 years and older [1]. The number of people aged 70 years and older rose from 8 to 14 million between 1990 and 2022, reflecting the overall ageing of the population [2]. Ageing is one of the most important risk factors for poor health. As the population ages, the number of factors associated with mortality in older people increases e.g. common diseases such as ischemic heart disease and cerebrovascular disease [3], but also cognitive impairment [4, 5] and lack of social networks [6, 7].

The prevalence and severity of cognitive decline increases with age [4, 5] and has been associated with a higher mortality risk in numerous studies [8–10]. The average survival time for individuals with cognitive impairment aged 75 and above is 4–8 years, with variations dependent on the severity of the impairment [11, 12]. This risk is further exacerbated by the presence of cognition-related comorbidities, multimorbidity, psychosocial changes, falls, and infections [10, 13]. Despite these insights, research on the specific impact of domain-specific cognitive impairments on mortality in older adults remains limited. One of the domains is semantic memory, which comprises the general knowledge about objects, facts and words that has been acquired over the course of a lifetime [14]. The hippocampus, which is typically affected first in the onset of cognitive decline [15], is responsible for semantic memory. Damage to the hippocampus leads to recognizable symptoms, such as memory problems [16, 17]. The second domain is executive function, which facilitates a range of cognitive processes, including planning and abstract thinking, as well as a variety of functional activities [18] and is a fundamental component of everyday life [19]. In older individuals, the loss of this function is associated with a decline in everyday functioning and an overall reduction in quality of life [18]. Executive ability is crucial for older people to cope with illness or stressful situations such as falls, thereby reducing mortality [18–20].

Social networks are a key factor influencing both mortality and cognitive decline [11, 21]. Findings from numerous epidemiological studies indicate that active engagement in social networks has a positive impact on survival in older adults [22–25]. The absence of social networks has been shown to impact mortality comparably to other established risk factors, including smoking, cardiovascular disease, ischemic heart disease, obesity and physical inactivity [24, 26]. In general, higher levels of social participation have been associated with a reduced risk of cognitive impairment in older people. Prospective studies have found that individuals who lack social networks exhibited a more than twofold increased risk of cognitive impairment relative to those with more extensive social networks [6, 7, 27, 28]. Fratiglioni et al. [29] demonstrated that the likelihood of developing dementia within a three-year period was nearly twice as high in individuals who resided alone and lacked close personal relationships. Social networks provide adults with access to a range of diverse and supplementary resources, which can be drawn upon in a variety of life circumstances [6]. They facilitate greater social integration in

society [30] and promote cognitively stimulating interactions, which in turn enhance well-being. On the other hand, due to morbidity and frailty, older adults are particularly dependent on their social networks and support to cope with everyday activities. Mainly due to the lower life expectancy of men, the care rate for older women is increasingly higher than for older men [31].

This study aims to explore how social networks influence the relationship between the two cognitive domains of semantic memory and executive function and mortality in older adults, with a focus on identifying vulnerable subgroups and understanding the protective role of social connections. We address the following research questions: Does the presence of a strong social network reduce mortality risk differently depending on cognitive status? Furthermore, does the combined effect of cognitive performance and social network integration on mortality vary across the two cognitive domains of semantic memory and executive function? We hypothesize that higher social integration (compared to lower) is associated with lower mortality risk, particularly in cognitively impaired individuals. Moreover, we expect this protective effect to be stronger in individuals with low executive functioning than in those with low semantic memory performance.

Materials and Methods

Data

The present study is based on data from the German National Cohort (NAKO Gesundheitsstudie, NAKO), a large-scale, prospective epidemiological cohort study in Germany [33]. Between 2014 and 2019, 205,000 individuals aged 20-69 years were recruited through a nationwide network of 18 study centers. All study participants were randomly selected based on age- and sex-specific strata from the mandatory population registers of the study areas [34]. Comprehensive questionnaires, clinical examinations and biomarker analyses provided information on demographics, health conditions, lifestyle factors, environmental exposures and social networks of the participants.

The data set used for the present analysis comprises 55,178 individuals aged 60 years and above (Supplement Figure S1). The observation period for the individuals began at the time of the baseline examination (2014-2019). Individuals were observed until their death ($N = 2,524$; 4.57%) or were censored at the end of the observation period in December 31, 2023 ($N = 52,654$; 95.43%).

Informed consent was obtained from all study participants. Ethics committees of all 18 study centers approved the NAKO study protocol.

Mortality follow-up

The NAKO mortality follow-up determines the date, place, type and cause of death for all deaths [35]. The deaths were coded in accordance with the 10th revision of the International Classification of Diseases (ICD) specifications [36]. The Competence Centre for Mortality Follow-Up (MoFU) conducted regular, case-related surveys of the vital status of the study participants in order to record the

deaths. This was also recorded via active follow-up, whereby participants were sent written questionnaires regarding health follow-up at two- to three-year intervals. The validation of the death information is carried out using a series of very extensive procedures, and the information is processed for linkage with other NAKO study parameters [37].

Outcome: All-Cause mortality

The participants of the study were observed through mortality follow-up until December 31, 2023. The year and month of death was documented for all deceased individuals.

Exposures: Cognition

Participants' cognitive performance was assessed at baseline by administering several neuropsychological test batteries. The test batteries comprised the Semantic Fluency Task, two Immediate Recalls of a 12-Word List, two Stroop Color-Word Tasks and a Delayed Free Recall of the 12-Word List. A detailed description of all test batteries can be found in the supplement, Table S1. To form cognitive domains for our analyses, we followed the work of Kleineidam et al. [38]. A factor analysis was conducted on the cognitive test batteries. The factor analysis led to the identification of two cognitive domains from the test batteries. Subsequently, variables from the test batteries were z-standardized and summed up to reflect the two cognitive domains. One cognition domain consisted of the two Immediate Recalls of 12-Word List and Delayed Free Recall of the 12-Word List (referred to as semantic memory). The other cognition domain was formed by summing the Semantic Fluency Task and the two Stroop Color-Word Tasks (referred to as executive functions). The results of the factor analysis can be found in the supplementary materials (Table S2). The cognitive domains were included in the analyses as metric variables. A low value indicates poor cognitive performance, while an increase, measured in standard deviations, indicates a higher cognitive performance.

Modifier: Social Network Index

The Social Network Index (SNI) from the NAKO data was used to analyze the social network. The SNI is a measure of the extent to which an individual is embedded in a social network. It included the dimensions of marriage/partnership, social contacts (close friends and relatives) and membership of social or religious groups. The construction of the index was based on the approach previously employed by Berkman and Syme [39]. For each dimension, a scoring system was utilized to quantify social integration. The points were aggregated to a total score and divided into four levels (from I to IV). A level of I represents the lowest degree of social embeddedness (social isolation), and a level of IV represents the highest number of contacts [40].

Covariates

We used age at baseline and its square (both centered around age 69), sex and study center, as an approximation of the current place of residence. The burden of comorbidity was calculated using an

adaptation of the Charlson comorbidity index, which is a weighted measure of health and morbidity burden [41]. An overview of the weights is provided in the supplement, Table S3. The NAKO provided the following self-reported comorbidities: stroke, myocardial infarction, systolic heart failure, peripheral arterial disease, diabetes mellitus, tumor disease, leukemia and AIDS.

The analyses were also controlled for the following socio-demographic factors that have been associated with cognitive abilities and language proficiency, which could potentially compromise the validity of the test results.

Education was classified according to the International Standard Classification of Education of 1997 (ISCED 97) [42]. Following Dragano et al. [43], education was classified into three categories: low educational attainment (primary education and lower secondary education), intermediate educational attainment (upper secondary education and post-secondary non-tertiary education) and high educational attainment (short-cycle tertiary education and Bachelor/Master/Doctoral or equivalent).

According to the International Labor Organization's Labor Force Concept [44], employment status is divided into the categories 'employed', 'unemployed' and 'inactive'. The group of employed persons includes employees, self-employed persons, family members helping out, persons in professional training, mini-jobs, 450-euro jobs and persons in a temporarily inactive employment relationship (maternity leave, parental leave). The group of unemployed persons comprises individuals who are not currently employed but are available to take up work and are actively seeking employment. The category of inactive persons includes those who have already left the labor market (pensioners) and individuals who are otherwise unavailable to the labor market [43]. Data regarding education and employment status were self-reported by the study participants.

The data regarding German language proficiency were collected through self-reporting and, in cases where German was not the native language, through the interviewer's assessment. The following categories were created: mother tongue German, mother tongue not German (very good/good German abilities), mother tongue not German (moderate), mother tongue not German (bad/very bad).

Furthermore, the analyzed models were controlled for lifestyle factors. Smoking history was classified using the cumulative risk measure of pack-years, where a pack-year is equivalent to smoking 20 cigarettes a day for one year. Alcohol consumption was categorized into three groups: no alcohol consumption, former alcohol consumption, and current alcohol consumption.

The analysis also included data on physical activity. In accordance with the WHO analysis guide, the Global Physical Activity Questionnaire (GPAQ) was applied to ascertain whether the WHO recommendation for physical activity of at least 600 MET minutes per week was met. The information was used as a binary variable for the analysis, indicating whether the WHO recommendation was full field or not.

The Body Mass Index (BMI) was calculated on the basis of anthropometric measurement and categorized according to the World Health Organization (WHO) classification [45]. An adult with a BMI of less than 18.5 kg/m² is considered underweight. A BMI between 18.5 and less than 25 kg/m² is

considered normal weight, a BMI of 25 to less than 30 kg/m² is classified as overweight, and a BMI of 30 kg/m² or higher is defined as obese [45].

Statistical Analyses

All variables, with the exception of age, were included in the analyses as time-invariant variables measured at baseline. Kaplan-Meier curves and death rates were calculated for the SNI and the two cognitive domains of semantic memory and executive functions. To examine the risk of social networks and cognition in relation to mortality, hazard ratios (HR) and corresponding 95% confidence intervals (95% CI) were estimated using Cox proportional hazards models [46]. For all analyses, the time to event began at the time of baseline and ended at the time of death or at the end of the observation period on December 31, 2023. First, we estimated stepwise adjusted models with semantic memory, executive function and SNI. Second, we included interaction terms between semantic memory and SNI as well as between executive function and SNI in two separate models. Each interaction effect was estimated three times, each time with a different reference group: low cognition and SNI level I (Ref. 1), moderate cognition and SNI level I (Ref. 2), and high cognition and SNI level I (Ref. 3) (Figure 1). To adjust for multiple testing, we applied Bonferroni-adjusted p-values [47]. All models were adjusted for age, sex, study centers, comorbidity index, education, employment status, mother tongue, smoker status, alcohol consumption, physical activity and BMI. All analyses were conducted using Stata 16.

For the sensitivity analysis, missing values in the exposure and covariates were imputed using multiple imputation by chained equations. Ten imputed data sets with 100 iteration steps were created using the *mi* package [48]. Cox proportional hazards models were then recalculated and pooled according to the combination rules of Rubin [49].

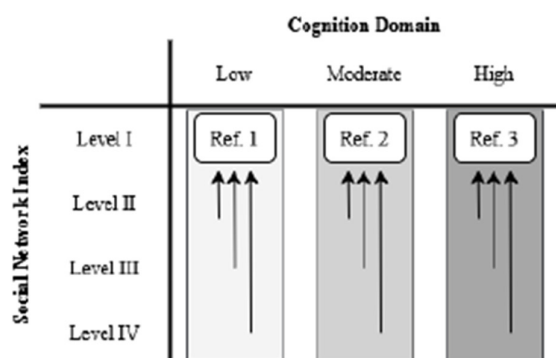


Figure 1 Schematic representation of the statistical analysis of interaction effects. Two separate models were estimated: one for the interaction between semantic memory and social network index, and another for the interaction between executive function and social network index. Each model was estimated three times with the following reference groups: low cognition and SNI level I (Ref. 1), moderate cognition and SNI level I (Ref. 2), and high cognition and SNI level I (Ref. 3).

Results

Descriptive Characteristics

The sample included 49.91% men and 50.09% women (Table 1). The majority of individuals exhibited moderate cognitive performance in both semantic memory (63.21%) and executive function (68.96%), while 6.69% had missing values in semantic memory and 7.55% in executive function. The data indicate that 30.00% and 32.43% of all individuals had a SNI level of II and III, while 7.94% have the lowest SNI level I. Only 2.53% have the highest SNI level IV, while 27.10% had missing SNI information. Over half of all individuals had no comorbidities (55.92%) and had attained a high level of education (52.65%). The majority of the study sample was inactive in terms of employment status (57.66%), 93.71% self-identified as German-speaking, 84.34% reported consuming alcohol, 86.50% demonstrated compliance with the WHO recommendation on physical activity, and 40.23% were overweight. The average number of pack-years was 10.86, with 7.13% of values missing.

Table 1 Baseline Characteristics of the study sample

	N	%
Sex		
Male	27,539	49.91
Female	27,639	50.09
Age at baseline		
60-64	26,281	47.63
65-69	24,513	44.43
70+	4,384	7.95
Social Network Index		
Level I (fewest contacts)	4,383	7.94
Level II	16,554	30.00
Level III	17,893	32.43
Level IV (most contacts)	1,396	2.53
Missing	14,952	27.10
Semantic Memory		
Low	8,080	14.64
Moderate	34,878	63.21
High	8,527	15.45
Missing	3,693	6.69
Executive Function		
Low	6,576	11.92
Moderate	38,051	68.96
High	6,384	11.57
Missing	4,167	7.55
Charlson Comorbidity Index		
Score 0	30,853	55.92
Score 1-2	18,072	32.75

Score 3-4	3,702	6.71
Score 5-12	525	0.95
Missing	2,026	3.67
Education		
Low	2,230	4.04
Middle	23,768	43.08
High	29,053	52.65
Missing	127	0.23
Employment status		
Employed	21,510	38.98
Unemployed	1,428	2.59
Inactive	31,818	57.66
Missing	422	0.76
Mother tongue		
German as mother tongue	51,706	93.71
Mother tongue not German; very good/good	2,034	3.69
Mother tongue not German; moderate	865	1.57
Mother tongue not German; bad/very bad	477	0.86
Missing	96	0.17
Pack-years (mean, (std. dev.))	10.86 (17.93)	
Missing	29,514	7.13
Alcohol consumption		
No alcohol consumption	2,167	3.93
Previous alcohol consumption	2,605	4.72
Current alcohol consumption	46,538	84.34
Missing	3,868	7.01
Physical activity		
No compliance with the WHO recommendation	6,461	11.71
Compliance with the WHO recommendation	47,729	86.50
Missing	988	1.79
BMI		
Normal weight	15,114	27.39
Underweight	283	0.51
Overweight	22,197	40.23
Obesity	15,439	27.98
Missing	2,145	3.89

N = 55,178; controlled for study centers. std. dev.: Standard deviation.

Source: NAKO baseline data and mortality follow-up.

Kaplan-Meier estimation

Figure 2 shows survival probabilities according to semantic memory, executive function, and SNI. Individuals with low cognitive function had the lowest survival probabilities, specifically 90.63% (95% CI: [89.28; 91.82]) for low semantic memory and 90.26% (95% CI: [89.33; 91.11]) for low executive function after ten years. Approximately 94% of individuals with a moderate categorization and 96%

with a high categorization within the cognitive domains survived (moderate: semantic memory: 94.49% [94.07; 94.88]; executive function: 94.41% [93.90; 94.88]; high: semantic memory: 96.06% [94.89; 96.96]; executive function: 95.56% [93.91; 96.76]). Following the observation period, 92.19% (95% CI: [90.49; 93.59]) of individuals with a SNI level I survived, while 94.40% (95% CI: [93.93; 94.84]) with a SNI level II survived. About 95% of those with a SNI level III or IV survived (level III: 95.60% [95.05; 96.09]; level IV: 95.40% [93.98; 96.50]).

Death rates

During the follow-up period (mean: 6.99 years), 2,524 deaths were recorded. The death rate (per 1000 person-years) for individuals with low semantic memory was 10.05 (95% CI: [9.26; 10.92]) and 11.79 (95% CI: [10.84; 12.83]) with low executive function (Table 2). The observed death rates with moderate semantic memory were 5.96 (95% CI: [5.67; 6.28]) and 5.78 for executive function (95% CI: [5.50; 6.08]). High semantic memory was associated with a death rate of 3.90 (95% CI: [3.43; 4.44]), and high executive function of 3.98 (95% CI: [3.43; 4.61]). In relation to SNI, the death rate was found to be highest among individuals with a level of I (8.46; 95% CI: [7.49; 9.55]). As the SNI level increased, the death rates decreased: 6.34 (95% CI: [5.89; 6.81]) among individuals with a level of II, 4.52 (95% CI: [4.17; 4.91]) among those with a level of III, and 5.52 (95% CI: [4.23; 7.21]) among those with a level of IV.

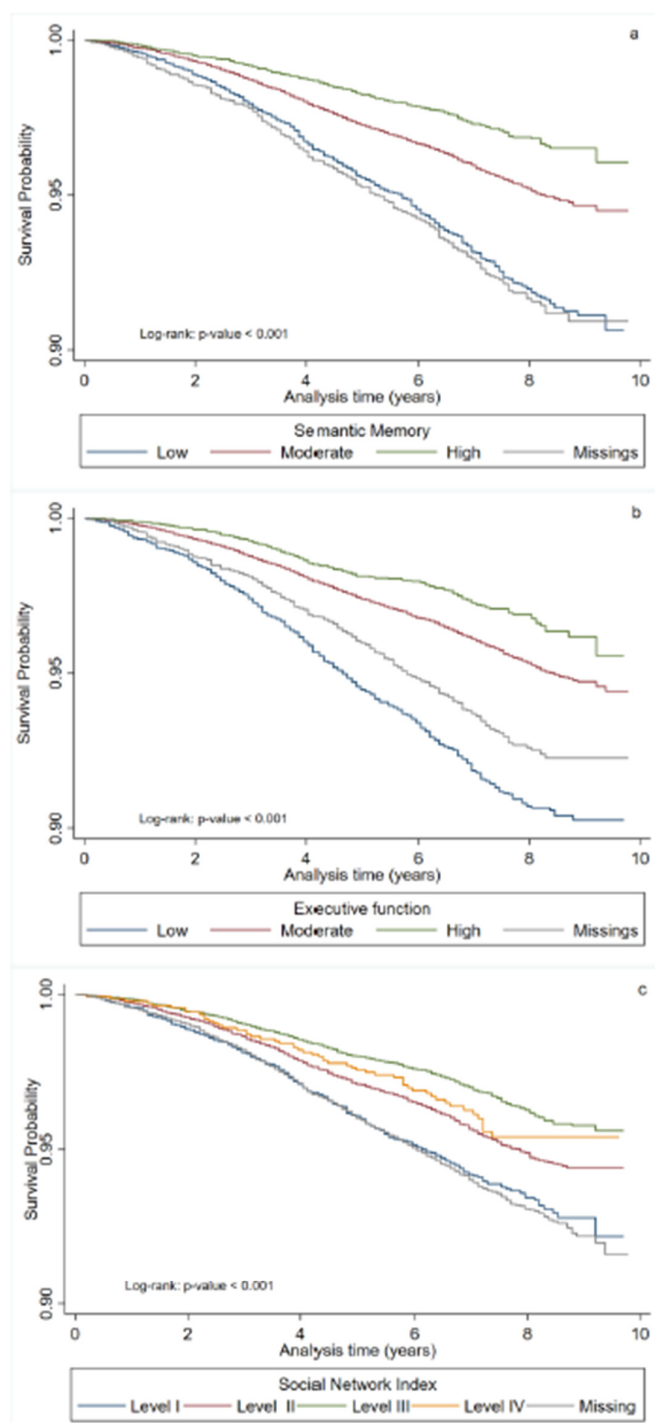


Figure 2 Kaplan-Meier plots of survival probabilities according to semantic memory (a), executive function (b) and Social Network Index (c). Source: NAKO baseline data and mortality follow-up.

Table 2 Death rates according to semantic memory, executive function and Social Network Index

	person-years	Deaths	Death rate (per 1000 person-years)	95% CI of Death rate	
Total	386046.92	2524	6.54	6.29	6.80
Semantic Memory					
Low	56306.42	566	10.05	9.26	10.92
Moderate	244662	1459	5.96	5.67	6.28
High	59724.71	233	3.90	3.43	4.44
Missings	25353.79	266	10.49	9.30	11.83
Executive Function					
Low	45617.42	538	11.79	10.84	12.83
Moderate	267381.46	1546	5.78	5.50	6.08
High	44494.42	177	3.98	3.43	4.61
Missings	28553.63	263	9.21	8.16	10.39
Social Network Index					
Level I (fewest contacts)	30627.54	259	8.46	7.49	9.55
Level II	116329.67	737	6.34	5.89	6.81
Level III	126651.79	573	4.52	4.17	4.91
Level IV (most contacts)	9776.83	54	5.52	4.23	7.21
Missings	102661.08	901	8.78	8.22	9.37

N = 55,178; Source: NAKO baseline data and mortality follow-up.

Model results

Table 3 illustrates the results of Cox proportional hazard models examining the association between cognition, SNI and mortality. Individuals with moderate semantic memory performance exhibited a 15% reduction in mortality risk ($HR = 0.85$, 95% CI = [0.76; 0.95]) compared with individuals with low semantic memory, and those with high semantic memory had a 25% reduction ($HR = 0.75$ [0.64; 0.89]) (Table 3, Model 1). The effect of moderate semantic memory was no longer statistically significant when executive function was considered (Table 3, Model 2). When SNI was introduced, the effect of moderate semantic memory remained insignificant, whereas executive function continued to show an association with reduced mortality risk. Specifically, moderate executive function was associated with a 28% reduction in mortality risk ($HR = 0.72$ [0.64; 0.81]), and high performance corresponded to a 33% reduction ($HR = 0.67$ [0.55; 0.81]) (Table 3, Model 3). Higher SNI levels were associated with reduced mortality risk, with only SNI level II and level III being identified as statistically significantly associated with a reduction in mortality risk (level II: $HR = 0.82$ [0.71; 0.95]; level III: $HR = 0.63$ [0.54; 0.73]). We confirmed the results in sensitivity analyses with the multiple imputed dataset (Supplement Table S4).

Interaction effects

Figure 3 shows the HR of the interactions between semantic memory and SNI and executive function and SNI according to cognitive status and indicates possible synergistic effects of the combination of two risk factors. An important pattern emerged for the interactions between the two cognitive domains and SNI levels: A U-shaped risk pattern emerged, with the lowest and highest SNI levels (I and IV) associated with higher mortality compared to moderate levels (II and III), except for those with high executive function, where there was no pattern by SNI level.

In the analyses of semantic memory, in all subgroups individuals with SNI level III had a lower mortality risk compared to individuals with SNI level I. Risk reductions ranged from 54% (low semantic memory), 28% (moderate semantic memory), and 44% (high semantic memory), respectively (Figure 3). Similar results were found for individuals with low and moderate executive functioning with risk reductions of 46% and 35%, respectively. For individuals with high executive functioning no risk reduction was found for people with SNI level III compared to people with SNI level I. Hazard ratios and 95% confidence intervals are provided in Supplement Table S5 and Table S6.

Table 3 Hazard ratios of memory function, executive function and social network index on mortality.

	Model 1		Model 2		Model 3	
	HR	95% CI	HR	95% CI	HR	95% CI
Semantic Memory						
Low	Ref.		Ref.		Ref.	
Moderate	0.85	0.76-0.95	0.91	0.81-1.01	0.93	0.83-1.04
High	0.75	0.64-0.89	0.83	0.70-0.99	0.86	0.72-1.02
Missing	1.09	0.90-1.30	1.08	0.86-1.36	1.06	0.84-1.33
Executive Function						
Low			Ref.		Ref.	
Moderate			0.70	0.62-0.79	0.72	0.64-0.81
High			0.63	0.52-0.77	0.67	0.55-0.81
Missing			0.80	0.64-1.00	0.82	0.66-1.03
Social Network Index						
Level I (fewest contacts)					Ref.	
Level II					0.82	0.71-0.95
Level III					0.63	0.54-0.73
Level IV (most contacts)					0.85	0.63-1.14
Missing					0.91	0.78-1.06

N = 55,178; HR = hazard ratio; 95% CI = 95% confidence interval; all models adjusted for age, sex, study center, comorbidity Index, education, employment status, mother tongue, smoker status, alcohol consumption, physical activity and BMI. Source: NAKO baseline data and mortality follow-up.

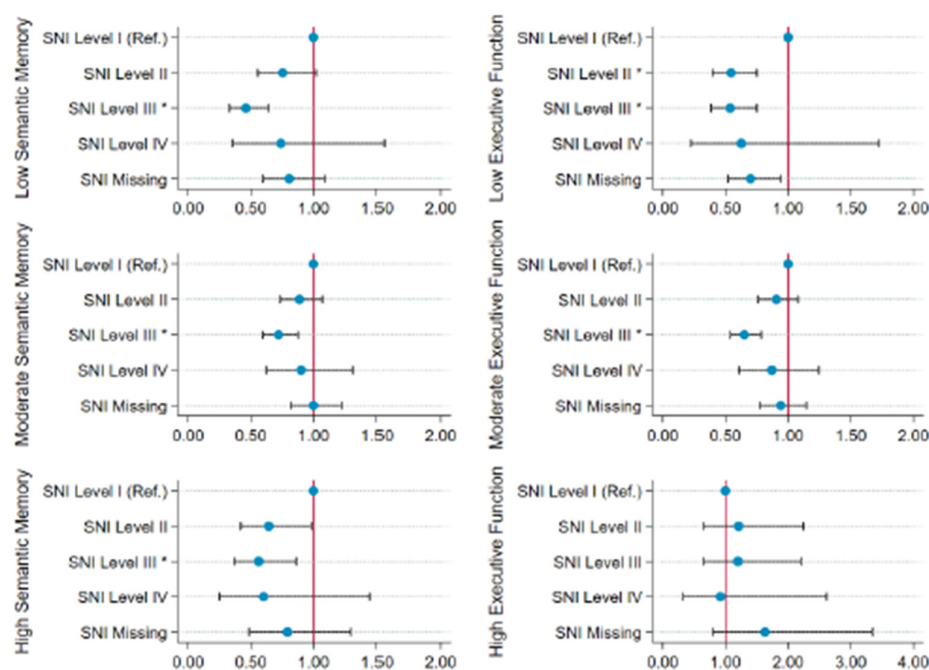


Figure 3 Hazard ratio and 95% confidence intervals of the same interaction term applied three times between cognition domains and social network index. N = 55,178; HR, hazard ratio; CI, confidence interval; * significant after Bonferroni correction for testing three times. All models were adjusted for age, sex, study center, comorbidity Index, education, employment status, mother tongue, smoker status, alcohol consumption, physical activity and BMI. Source: NAKO baseline data and mortality follow-up.

Discussion

Our study identified indication of U-shaped patterns of mortality risk in the interactions between semantic memory and SNI and executive function and SNI in relation to cognitive status. Specifically, when combined with SNI level III, mortality risk was significantly lower than the individual risks associated with SNI and cognitive function. In contrast, individuals with the lowest (level I) and highest (level IV) social network integration faced the greatest risks. Interestingly, this U-shaped pattern was absent in individuals with high executive function, as SNI levels were not associated with mortality.

It has already been established that executive function includes the processing of goal-directed behavior and the control of complex cognitive processes, particularly in non-routine situations [50, 51]. It encompasses a range of abilities, including flexibility of thought, social rule-following, the capacity to monitor one's own behavior, impulse control, task adaptation and problem solving, abstract thinking, creativity, processing speed, and visuospatial attention [20, 52–54]. In older adults, all of these areas were of critical importance for the ability to cope with the demands of everyday life, including problem solving, adapting to new situations, and intuitive processes such as walking [52, 55]. The progression of cognitive decline has been associated with an increased likelihood of falls, multimorbidity, and infections. Patients with executive decline may not behave in an appropriate manner in the event of multimorbidity or infection. This could lead, for example, to an increased prevalence of pneumonia, urinary tract infections, bone fractures or organ failure, which increase the mortality risk of these individuals, especially in the presence of cognitive problems [13]. We observed a lower mortality risk for higher social network integration, which is in accordance with the assumption that the quality of life gained through networks may reduce mortality risk. Individuals with moderate and low executive function benefited from the presence of a network, while individuals with high executive function showed no effect of the presence of a social network on mortality risk. These people may still have been cognitively healthy enough to manage their daily lives and problems without additional support. It has already been shown that social networks provide an opportunity to stimulate semantic memory through conversation [57] and thus they may slow decline at all stages of memory impairment. In addition, further studies were able to show that people that are in contact with caregivers have improved quality of life through the fact that caregivers remind people of appointments or assist them with daily activities, which may explain a positive impact on mortality risk.

Social contacts create a framework for health-related behavior and health norms, as well as access to health promotion [58, 59]. The interaction with social contacts was demonstrated to stimulate cognitive functions and counteract the associated deterioration process [60]. Physical activation through visits to family, friends, or social or religious institutions has also been positively associated with cognitive performance, thereby counteracting the process of its decline [60].

Studies have revealed that the composition of social networks may change with age. While friendship networks tend to become less important, family networks remain relatively stable [61]. From the age of 60 to 65, networks undergo a reduction in size of approximately one contact per decade on average [61, 62]. As health restrictions increase, those affected tend to withdraw from social activities [61]. The lack of a supportive social network could be a source of vulnerability, particularly in terms of health, which in turn may increase the risk of mortality.

Based on the possible mechanisms of the relationship between social networks, cognition and mortality known from the literature, the results of the analyses were surprising, showing that SNI level IV did not reduce the risk of mortality. One possible explanation of this results could be the small number of observations. Another could be that those individuals with SNI level IV were already very seriously ill. The effect of being "seriously ill" was considered by controlling for comorbidities. However, the comorbidity index used is incomplete and was adapted from the Charlson index. Due to their health status and need for support, they already had a strong social network to take care of them. Severe cognitive impairment, dementia, or comorbidities such as cardiovascular disease, greatly increased the risk of death [63], which cannot be reduced by a strong social network. In addition, a level IV network could involve too many contacts for the person concerned. Interpersonal relationships usually helped to cope with stress by enabling them to fulfill basic needs [64].

It is important to acknowledge the limitation that, although NAKO utilizes a large sample from the general population in Germany, the participants were predominantly older and tended to have a higher level of education than the general German population [43]. These sociodemographic characteristics are typically associated with a higher willingness to participate in health studies [65]. Furthermore, a health selection was observed in which the study group had a low prevalence of comorbidities, indicating an overall milder disease profile. At present, only data from the baseline survey (2014-2019) were available, with all control variable data included in the analyses at that time. It could be possible that the comorbidity structure may be underestimated, because they were only measured at baseline, whereas the observation period extended several years beyond, and new comorbid conditions that developed during the follow-up period were not captured. As the data on social networks was self-reported, they may have been influenced by social desirability, leading to an overestimation. However, the questions were not asked in an interview. This may have reduced the risk of bias. In addition, the SNI measured only personal social contacts, such as family, friends, and leisure groups, and excludes professional contacts. Professional contacts may have compensated for missing family contacts due to loss or relocation. This may have underestimated the true number of social contacts. To counteract this, we controlled the analyses for employment status. Further analyses are necessary to analyze the exact effects of the individual social groups and to uncover possible different influences.

Another potential limitation of our findings arises from the mortality follow-up process. The data were obtained at regular intervals through mortality surveys. Due to the temporal discrepancy between the actual time of death and the time of inquiry, individuals could still be classified as alive in the study despite having already died. To address the issue of misclassification of deaths and ensure a low misclassification rate, we limited the observation period to the end of 2023. The death rate observed in this sample is notably lower than in the total German population [66]. This disparity could be attributed to the bias that the NAKO sample consists of individuals who are, on average, better educated, and healthier. However, mortality monitoring also presents promising avenues for further analysis. The next follow-up examinations and surveys planned by NAKO will provide an opportunity to obtain more comprehensive longitudinal data that will also reveal changes in cognitive status and SNI and will allow for a better understanding of the progression and the pathway of the disease.

Conclusion

Our study highlights the critical implications of low social integration for older individuals with impaired cognitive functions. The findings emphasize the importance of fostering social network integration for this population to reduce mortality risk, highlighting that low cognition and limited social integration jointly pose a greater mortality risk than each factor alone. Encouraging greater societal and social network involvement in this group may mitigate their elevated mortality risk.

Future research could delve into individual dimensions of social networks in relation to various cognitive domains to uncover more nuanced associations. A more detailed investigation into the causes of death would also provide deeper understanding. Identifying the protective and detrimental aspects of (the lack of) social integration could inform targeted interventions to positively delay cognitive decline and improve mortality outcomes in older adults.

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Abbreviations

BMI – Body Mass Index

CI – confidence interval

GPAQ - Global Physical Activity Questionnaire

HR – Hazard ratio

ICD - International Classification of Diseases

ISCED 97 - International Standard Classification of Education of 1997

MoFu – Mortality Follow-Up

NAKO - German National Cohort

SNI – Social Network Index

WHO - World Health Organization

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Author Contributions

ER developed the research questions. LK, IMV, MBS, BS, RM, LP, NO, JKH, CJKT, WL, KW, ML, HB, OR and BB were involved in data collection. DG prepared the data. ER conducted the data analyses and drafted the manuscript. ER contributed to the interpretation of the data. All authors read and approved the final manuscript.

Ethics approval

The German National Cohort study is performed with the approval of the relevant ethics committees, in accordance with national law and in accordance with the Declaration of Helsinki of 1975.

Consent to participate

Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

A. Supplementary Files

Indication of own contribution for collaborative work with multiple authors

Study I:

Rakuša, E.; Fink, A.; Tamgüney, G.; Heneka, M. T. & Doblhammer G. (2023): Sporadic Use of Antibiotics in Older Adults and the Risk of Dementia: A Nested Case–Control Study Based on German Health Claims Data. *Journal of Alzheimer’s Disease* 93 (2023) 1329–1339. doi: 10.3233/JAD-221153

Elena Rakuša’s own contribution: formulating the research question: 50%, designing the study: 50%, conducting and analyzing the study: 80%, writing the texts: 90%.

With my signature I confirm the above assessment of my co-author Elena Rakuša’s contribution to our collaborative work.

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Indication of own contribution for collaborative work with multiple authors**Study II:**

Rakuša, E.; Reinke, C.; Doblhammer, G.; Radbruch, L.; Schmid, M.; Welchowski, T. (2025): Dementia as a predictor of palliative care: Uncovering patient patterns based on German claims data. BMC Palliat Care 24, 46 (2025). doi: 10.1186/s12904-025-01672-y

Elena Rakuša's own contribution: formulating the research question: 50%, designing the study: 60%, conducting and analyzing the study: 80%, writing the texts: 90%.

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Indication of own contribution for collaborative work with multiple authors

Study III:

Rakuša E., Georges D., NAKO Consortium, Doblhammer G.: Exploring the Impact of Social Networks and Cognitive Function on All-cause Mortality in Older Adults: Insights from the German National Cohort (NAKO)

Elena Rakuša's own contribution: formulating the research question: 80%, designing the study: 90%, conducting and analyzing the study: 100%, writing the texts: 90%.

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Eidesstattliche Versicherung

Ich erkläre hiermit, dass ich die vorliegende Arbeit ohne unzulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe; die aus fremden Quellen direkt oder indirekt übernommenen Gedanken sind als solche kenntlich gemacht.

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Elena Rakuša