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Patient-reported & Health Economic Outcomes for Low-value Medications in Patients Living with Dementia

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Overview of the articles

This thesis is based on data from the DelpHi-MV study (Dementia: life- and person-centred help in Mecklenburg-Western Pomerania), which was performed in cooperation with and funded by the German Center for Neurodegenerative Diseases and the University Medicine Greifswald, and consists of three articles published in the following peer-reviewed journals:

1) **Platen M**, Fleßa S, Rädke A, Wucherer D, Thyrian JR, Mohr W, Scharf A, Mühlichen F, Hoffmann W, Michalowsky B. Prevalence of Low-Value Care and Its Associations with Patient-Centered Outcomes in Dementia. J Alzheimers Dis. 2021;83(4):1775-1787. doi: 10.3233/JAD-210439. PMID: 34459396; PMCID: PMC8609693. (**IF 2021: 4.160**)

2) **Platen M**, Flessa S, Rädke A, Wucherer D, Thyrian JR, Scharf A, Mohr W, Mühlichen F, Hoffmann W, Michalowsky B. Associations Between Low-Value Medication in Dementia and Healthcare Costs. Clin Drug Investig. 2022 May;42(5):427-437. doi: 10.1007/s40261-022-01151-9. Epub 2022 Apr 28. PMID: 35482178; PMCID: PMC9106620. **(IF 2021: 3.580)**

3) **Platen M**, Flessa S, Teipel S, Rädke A, Scharf A, Mohr W, Buchholz M, Hoffmann W, Michalowsky B. Impact of low-value medications on quality of life, hospitalization and costs - A longitudinal analysis of patients living with dementia. Alzheimers Dement. 2023 Mar 11. doi: 10.1002/alz.13012. Epub ahead of print. PMID: 36905286. (**IF 2021: 16.655**)

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List of abbreviation

AOK	Allgemeine Ortskrankenkasse
B-ADL	Bayer Activities of Daily Living Scale
CCI	Chalson comorbidity index
CI	Confidence interval
DelpHi-MV	Dementia: life- and person-centred Help in Mecklenburg-Western Pomerania
DGIM	Deutsche Gesellschaft für Innere Medizin e.V.
DZNE	Deutsches Zentrum für Neurodegenerative Erkrankungen e.V.
FORTA	Fit fOR The Aged
GDS	Geriatric Depression Scale
GP(s)	General practitioner(s)
HRQoL	Health-related quality of life
ICD-10	10th revision of the International Statistical Classification of Diseases and Related Health Problems
Lvm	Low-value medications
MAX	Maximize
MMSE	Mini-Mental State Examination
OR	Odds ratio
PIM	Potentially Inappropriate Medication
PRO	Patient-reported outcomes
PwD	Persons living with dementia
QoL-AD	Quality of Life in Alzheimer's Disease
SD	Standard deviation
SF(-12/-36)	(12-/ 36-Item) Short-Form Health Survey
U.S.	United States
WHO	World Health Organisation

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1. Introduction

One of the main goals of health economics is to achieve the best possible care with the available resources or, more specifically, to increase the efficiency of the health care system by an optimal allocation of scarce resources to the production processes that guarantee the best possible quantity and quality of health care services [1].

A recent United States (U.S.) study shows that up to 30% of annual health care spending is wasted, equivalent to US$935 billion [2]. Over US$100 billion can be attributed to low-value care and overuse [2]. Low-value care and overuse are defined as care or services unlikely to benefit patients, cause harm, and waste scarce health care resources such as potentially inappropriate medications or unnecessary tests and procedures [2-4]. Accordingly, low-value medications (Lvm) represent overuse in pharmaceutical care.

Although no comparable studies or systematically collected data on overuse in Germany are available, evidence suggests that overuse and low-value care are also present in the German health care system [5]. The following will explain why it is necessary to address low-value care in the German health care system and to develop strategies to reduce the provision and use of low-value services.

Health care expenditures in Germany are steadily increasing. According to the German Federal Statistical Office, the volume of health care expenditures in 2020 most recently amounted to €441 billion or €1.2 billion per day, or €5,298 per inhabitant, which corresponds to an increase of 6.5% compared with the previous year and now accounts for a share of 13.1% of gross domestic product [6]. With 54.8%, statutory health insurance accounted for more than half of health care expenditure [6]. Figure 1 outlines the increase in health care spending from the turn of the millennium until 2020.

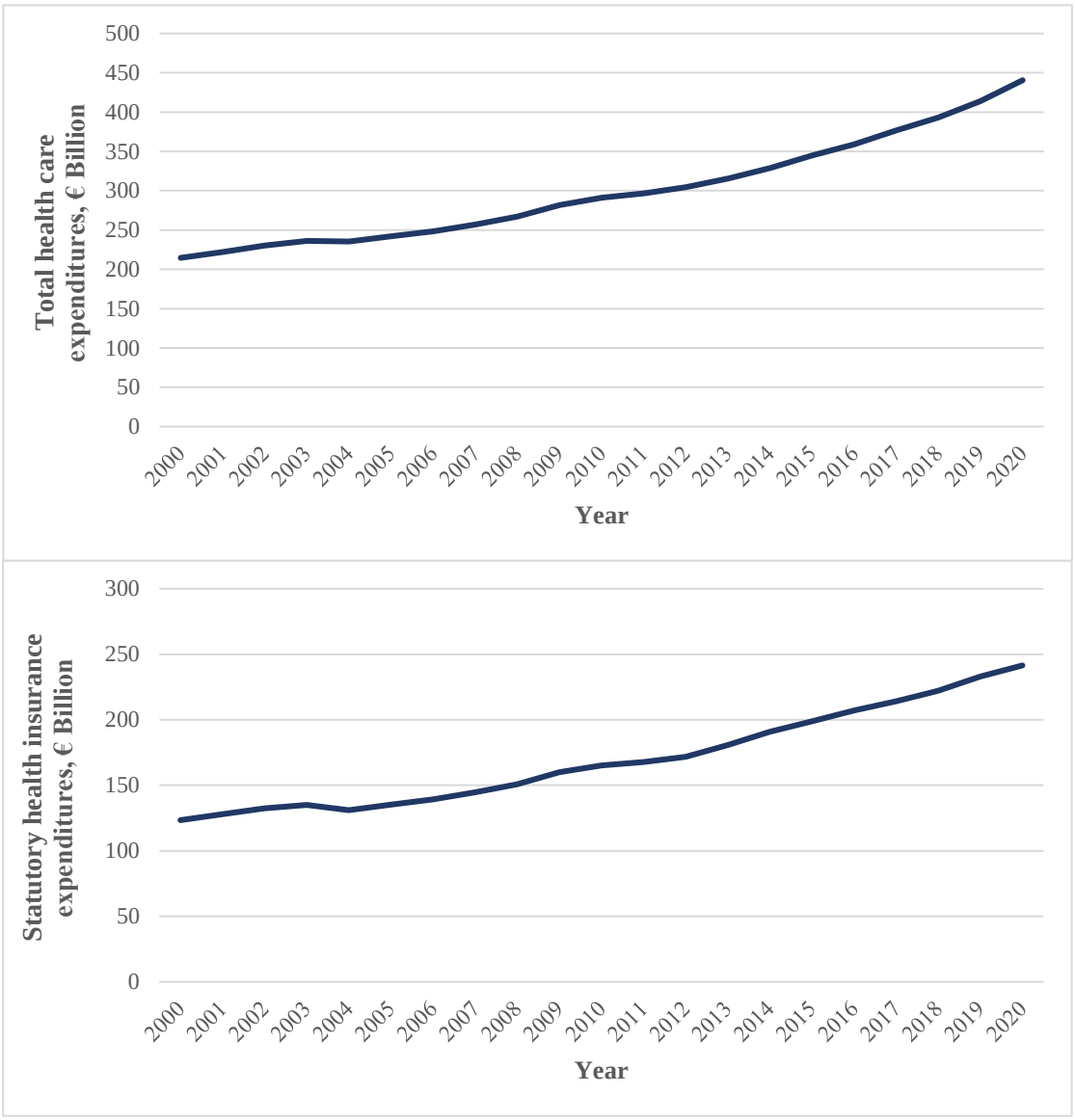


Figure 1: Total health expenditures & Health expenditures by statutory health insurances between 2000 and 2020 for Germany.

Source: Own figure based on Federal Statistical Office [6-8].

Hospitals and pharmaceuticals are among the main cost drivers, accounting for 26% or 15% of health care spending, respectively [7, 8]. Figure 2 summarizes the development between 2000 and 2020 for both categories. However, the question is not whether we are spending too much money but whether these financial resources are allocated to high-value resource uses [9].

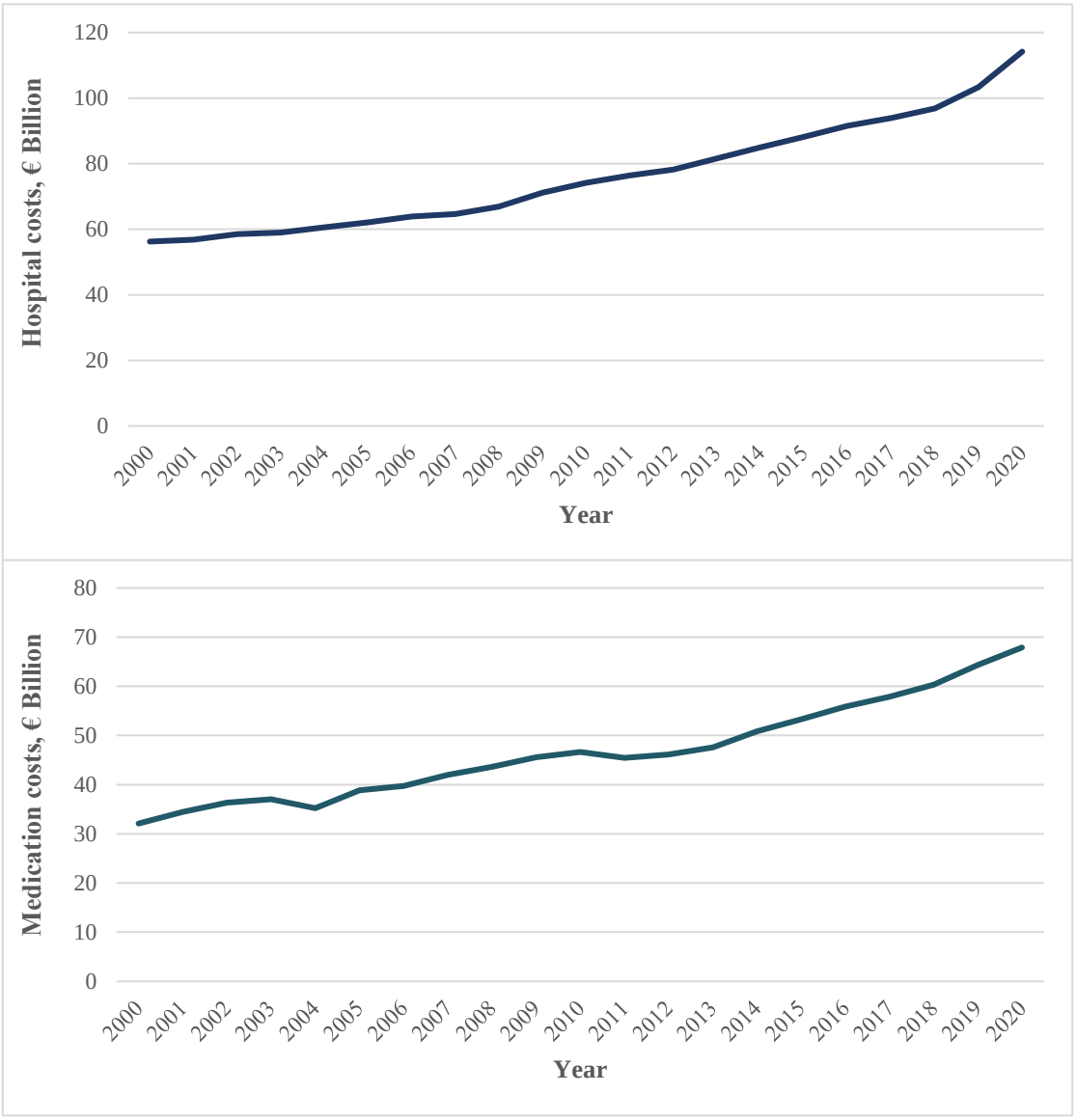


Figure 2: Total health expenditures by hospitals & medications between 2000 to 2020 for Germany.

Source: Own figure based on Federal Statistical Office [7,8].

Another challenge facing the health care system results from the consequences of demographic change. The population's ratio of young to older people is shifting in favour of older people [10]. This shift reduces the potential workforce that contributes to the financing of the health care system [11]. Furthermore, the cost pressure increases because the probability and frequency of illnesses increase with increasing years of life [10, 11]. However, demographic developments are not the only reason for changes in the demand for health care services. The economic development of a

country represents an additional influencing factor [12]. For example, chronic degenerative diseases have replaced infectious diseases as the most important cause of morbidity and mortality, especially in Western societies [12, 13]. This circumstance, in turn, gives rise to new patient needs, which must be met by realigning the health care system.

One of the most common age-associated chronic degenerative diseases is dementia. The latest figures from the German Alzheimer Society indicate that approximately 440,000 persons over 65 in Germany were newly diagnosed with dementia in 2021 [14]. The total number of persons living with dementia (PwD) for 2021 is estimated at 1.8 million and could increase to 2.8 million in less than 30 years [14]. According to the German Federal Statistical Office, disease costs for dementia already amount to more than €20 billion annually [15]. Additionally, taking informal care into account, PwD caused total societal excess costs of €33,188 per capita compared to persons over 65 without dementia [16].

Although this large amount of financial resources is devoted to caring for PwD, this effort is already contrasted with many unmet needs [17]. Just around 40% of patients screened positive for dementia receive a diagnosis at all [18], resulting in just 30% receiving an antidementia drug [19, 20], only 37% having access to non-drug services recommended by guidelines [21], and over 93% having drug-related problems [22]. These figures offer evidence of the inefficient use of resources in dementia care.

The approach to reducing low-value care promises an increased scope of action for better care for PwD using the same resources. Although media reports of the last 1.5 years have raised hopes [23, 24], there is currently no prospect of a cure for PwD, which is why they need the best possible care.

An important pillar of care for PwD and their comorbidities comprises pharmaceutical care contributing to 25% of health care costs in dementia from the payer perspective [19]. Previous studies have shown that providing Lvm to PwD is common, particularly potentially inappropriate medications [25-27]. Beyond Lvm, across the entire spectrum of low-value care, previous research focuses mainly on the prevalence of individual services and less on mapping the potential for harm at the patient and

system level because studies often rely on claims data [28, 29]. In addition, there is a lack of reported longitudinal effects of Lvm on patient-relevant outcomes.

Therefore, this study aimed to determine, within primary data analyses, the prevalence of PwD receiving Lvm, to identify associations between Lvm and health-related quality of life (HRQoL), hospitalizations, and direct medical care costs, and finally to demonstrate the impact of low-value medications on these endpoints over 24 months.

Following this introduction, the concept of low-value care is introduced and viewed through the lens of health care performance management (2.1.). The starting point is the efficiency criterion (2.1.1.). In addition, the system model of health care service production is outlined (2.1.2.), and a framework model for assessing the quality of health care services is provided (2.1.3.). These elaborations are followed by the medical background of dementia, with a focus on aetiology, epidemiology, and diagnosis and treatment (2.2.). Subsequently, the dementia-related patient-reported outcomes studied (HRQoL, hospitalizations, and direct medical care costs) are discussed in more detail (2.3.). The background concludes with the presentation of published national and international studies, followed by an elaboration on the research gap (2.4).

Within the framework of the methodology, the DelpHi-MV study (Dementia: life- and person-centred Help in Mecklenburg-Western Pomerania) [30], from which the data are taken, is first described (3.1.). Furthermore, it is explained how and which data were collected (3.2.). Finally, the statistical procedure for the analyses is presented (3.3.).

A report of the results of the cross-sectional and longitudinal analyses follows. Descriptive statistics are presented, including group comparisons regarding sociodemographic and clinical characteristics and the investigated outcomes by Lvm intake (4.1.1. - 4.1.2. and 4.2.1. - 4.2.2.). The associations and effects of Lvm intake are then highlighted (4.1.3. and 4.2.3.). Finally, the analysis results are discussed against the background of already published studies (5.1.) and action-guiding impulses for the German health care system are derived from them (5.2.). The last section concludes (6).

2. Background

The following section introduces the concept of low-value care in health care and elaborates on the basic information on dementia. Afterwards, the dementia-related patient-reported and health economic outcomes based on the research question will be presented before the international and national studies, and associated research gaps will be outlined.

2.1. Low-value services in health care

The term low-value medications (Lvm) comprises the use and prescription of medications classified as low-value and is a subsidiary category of low-value care; hence, the term low-value care will be derived first. The theoretical framework for this approach is provided by performance management or, more specifically, the theory of producing health care services. It differs from industrial approaches by distinguishing between quality and quantity components [31]. Since health care services are central, the term low-value services will also be used.

2.1.1. Efficiency criterion in health care

The starting point of the derivation is the efficiency criterion, which is the decisive factor for the classification as low-value. However, focusing on the efficiency criterion is insufficient to address the concepts of overuse and low-value care. The actual meaning of the two concepts results mainly from the opposite, namely waste.

2.1.1.1. Efficiency in health care

Efficiency in health care generally describes the best possible use of resources to improve the health of individuals, specific groups, or populations under conditions of scarcity [1]. In this context, the resources used are termed input, and health improvement (and maintenance) is termed output [32]. The process involving input transformation into outputs is called production [31]. The condition of scarcity requires dealing according to one of the two principles of the production process [1]:

1. The minimum principle aims to achieve a fixed output with minimum resource input.
2. The maximum principle aims to achieve the maximum output with a fixed resource input.

The production process can also be represented as an optimization task ensured by the health care system as follows [1, 32, 33]:

$$E = \frac{Output}{Input} \rightarrow MAX!$$

According to the World Health Organization (WHO), "health is a state of complete physical, mental, and social well-being and not simply freedom from disease and infirmity" [34]. Consequently, the output of the production process represents health goods that are consumed or used to contribute to the health state, either by improving or maintaining it [35]. Health care goods can be material goods, such as drugs or medical aids, but can also include services, such as diagnostics or certain medical treatments [32]. Furthermore, health care goods are assigned to credence goods because they are i) rarely used, ii) patients have little personal experience and expertise, and iii) decisions are usually irreversible [32]. Finally, the health goods, like other goods, are offered, demanded and coordinated in health markets.

2.1.1.2. Waste in health care

Usually, waste is defined in the health economics literature as the opposite of efficiency [33]. With recourse to both principles outlined above, resources are wasted if the output quantity is lower than expected for a given resource input or if more resources are required than could be assumed for a given output.

In addition, authors Donald Berwick and Andrew Hackbarth [3], in their Special Communication "Eliminating Waste in US Health Care" in the Journal of the American Medical Association in 2012, distinguished the following six categories of potential waste in health care:

1. *Failures of Care Delivery*: According to the authors, this category describes waste that arises from inefficient service delivery or lack of adaptation of known innovative forms of care (i.e. the state-of-the-art).
2. *Failures of Care Coordination*: This category includes costs that may result, for example, from fragmentation and thus sectorization of the health care system.
3. *Overtreatment*: This refers to care that does not benefit patients according to scientific evidence and their preferences.
4. *Administrative Complexity*: This refers to inefficient regulatory frameworks that result in unnecessary bureaucracy and, for example, ensure that the resources of medical staff are tied up inappropriately due to documentation requirements.
5. *Pricing Failures*: These include cases where, for example, prices for services far exceed production costs plus a reasonable profit.
6. *Fraud and Abuse*: This category includes, for example, billing fraud.

Based on a literature review, Shrank et al. [2] estimated cost ranges for each category. Accordingly, U.S. health care's estimated annual cost of waste is US$760 billion to $935 billion [2]. These figures represent about 25% of annual health care spending [2]. The largest share is assigned to the *Administrative Complexity* category, estimated at US$265.6 billion [2]. The *Pricing Failures* category is attributed to the second highest costs, ranging from US$230.7 billion to US$240.5 billion [2]. This figure is followed by the *Failures of Care Delivery* category, which is between US$102.4 billion and US$165.7 billion [2]. *Overtreatment or low-value care* is between US$75.7 billion and US$101.2 billion [2]. Furthermore, between US$58.5 billion and US$83.9 billion are attributed to the *Fraud and Abuse* category [2]. Finally, Shrank et al. [2] estimate that the *Failure of Care Coordination* category accounts for the smallest share of health care waste at US$27.2 billion to US$78.2 billion. Figure 1 summarizes the estimated cost of waste in U.S. health care for each domain according to Shrank et al. [2].

Although, according to Donald Berwick and Andrew Hackbarth [3], the six categories do not claim to be exhaustive and lack selectivity in some cases, they allow for a more differentiated conceptual perspective on the term waste.

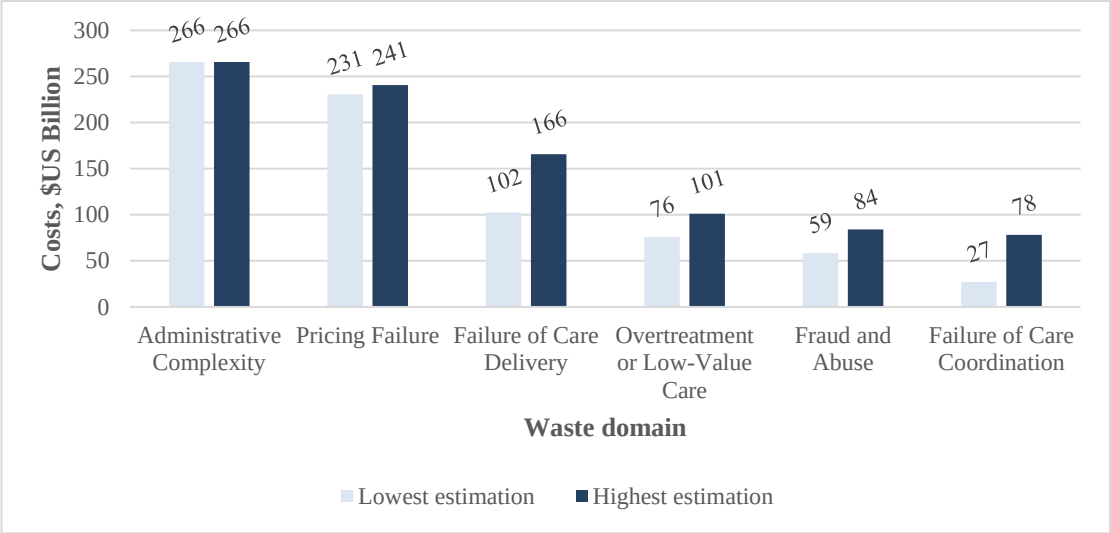


Figure 3: Cost estimates by waste domain for the U.S. health care system.

Source: Own figure based on Shrank et al. [2].

2.1.1.3. Concepts of overuse and low-value care

While Berwick and Hackbarth [3] only refer to *overtreatment* in their categorization, Shrank et al. [2] add low-value care to this category. A commonly used definition comes from Elsaugh et al. [36], who define *low-value care* as an intervention that has been shown to provide no or very little benefit to patients, where the risk of harm exceeds the likely benefit, or, where additional costs of the intervention are not outweighing additional benefits.

Verkerk et al. [37] point out that other definitions of *low-value care* can also be found in the literature, each addressing different elements, but no definition includes all elements. They intend to follow a definition which adds a societal perspective to the patient- and service-centred perspective. They refer to *low-value care* as "care that is unlikely to benefit the patient given the harms, cost, available alternatives, or preferences of the patient" [37].

In addition, other terms such as *overtesting*, *overdiagnosis*, *overutilization* or *overmedicalization* can be found in the literature [38, 39]. Carter et al. [39] problematize the diversity of terms that overlap and are interrelated because these concepts describe specific services on the care pathway that are mutually supportive, sequential, interdependent, or caused by each other. Carter et al. [39] argue for

overarching terms such as "*too much medicine*" or "*less is more medicine*" that encompass all concepts and are also easily understood in public relations. Brownlee et al. [38] use the term *overuse* for this purpose and break it down to the following definition: “Provision of medical services that are more likely to cause harm than good”.

The term *overuse* (and its opposite, *underuse*) is also used in German-language research. It describes care with non-indicated services, or with services without sufficiently assured net benefits (*medical overuse*), or with services with only minor benefits that do not justify the costs, or provided in an inefficient, i.e. uneconomic, form (*economic overuse*) [40]. In contrast to the above definitions, a distinction is explicitly made between *medical* and *economic overuse*. However, this definition lacks the harm component, which is why *misuse* is also used in the German discourse. *Misuse* includes any care that causes avoidable harm [40].

2.1.2. System model of health service production

Health systems, their respective subsystems and stakeholders have the basic function of producing health [31]. As already elaborated, the representation of efficiency as a quotient of input and output does not fulfill this function since the output is not health but a health good or health service. However, the extended system model of the production of health services provides a remedy for the analysis [12].

Figure 2 illustrates the system model of health services production. The production of the health care service is at the center of the model. The transformation requires resources or *inputs* society provides, such as labour, capital, operating resources, materials or information [1, 12, 32, 41]. In the ideal case, various *inputs* are efficiently combined during the transformation process into *outputs*, i.e. inputs and outputs are appropriately balanced [1, 12, 32, 41]. These *outputs* represent specific medical or nursing services or products. Each utilization of health services affects the patient's health status [1, 12, 32, 41]. The effect at the patient level is referred to as the *outcome* [1, 12, 32, 41]. As a whole, the outcomes affect society. The so-called *impact* is reflected in population health and, for example, in the prosperity of a national economy [1, 12, 32, 41]. Therefore, the model is characterized by feedback. Society

only provides the resources or *inputs* if the system's function is fulfilled, i.e. if a positive contribution is made to achieving the goals from the perspective of the service providers, patients and society. Finally, the model is surrounded by a system that influences both the supply and demand sides, or the function and criteria for fulfilling the function, through factors such as epidemiology, demographics, or economic strength [1, 12, 32, 41].

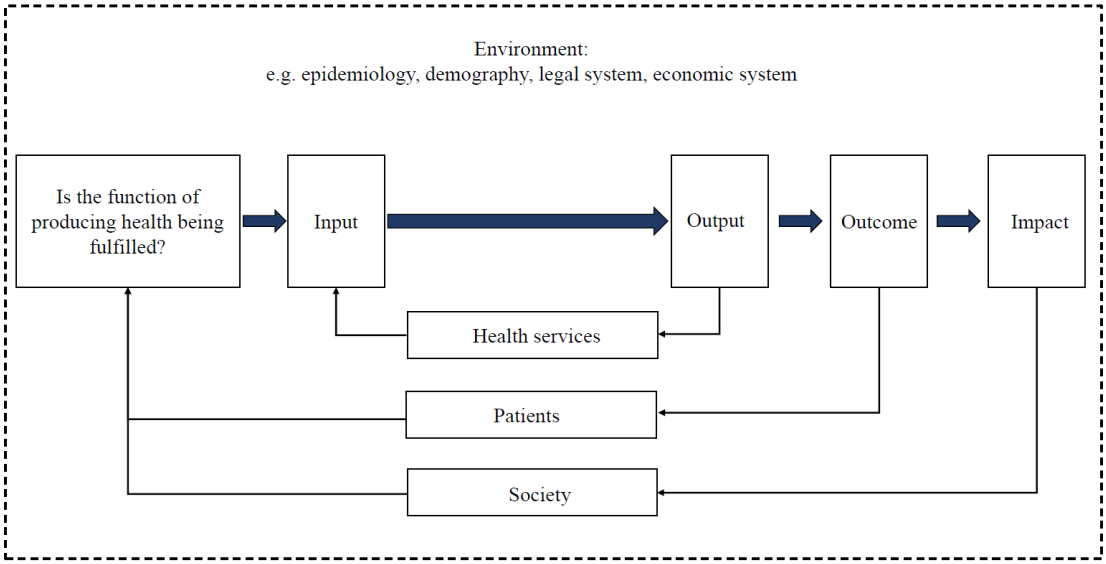


Figure 4: System model of health services production.

Source: Own figure based on Fleßa [32].

This expanded model underscores the ethical, economic, and political importance of efforts to curb the presence of low-value services [36].

2.1.3. Quality of health services

Because low-value care and overuse describe quality problems, the following section will first outline Donabedian's framework model, which explicitly focuses on the appropriate evaluation of health care services. In addition, approaches will be presented on how quality can be measured in concrete terms.

2.1.3.1. Donabedian model

Due to different reference points (e.g. objective vs. subjective, product-oriented vs. customer-oriented), no consistent definition of quality exists [32]. Hensen [42] describes quality as complex-multi-perspectival, and it can thus only be evaluated via contextual reference. In addition, requirements must be defined to determine a target value, whereby quality ultimately represents the degree of fulfillment of these requirements and is to be understood as a target-actual difference [42].

In order to be able to analyze the quality, nevertheless, a framework model is needed. The Donabedian model builds on the proposed model for the production process and is therefore suitable for this purpose [31, 32, 42]. On the one hand, it distinguishes between the domains of *structural*, *process* and *outcome* quality, and on the other hand, it links the individual domains so that each domain is necessary but insufficient for its own [31, 32, 42].

Following the service production model, all input variables are considered under the domain of *structural quality*, which includes all personal, material and organizational prerequisites necessary for the production process [42]. *Process quality* encompasses the actual process of service provision, including all sub-processes and support processes [42]. The focus of *outcome quality* is on results [42]. However, this requires distinguishing between the production process's actual outcome, the service's effect on service recipients, and long-term effects beyond individuals, as described in the previous section [32].

Low-value care is also described as *indication quality* that provides information on the appropriateness of a diagnostic, medical, or nursing service given the symptoms or diseases indicated [43]. *Indication quality* is considered a special case of *process quality* [31, 43]. While *process quality*, in the narrower sense, asks whether things are being done right, indication quality asks beforehand whether the right things are being done [31]. Figure 3 outlines the Donabedian model, including indication quality.

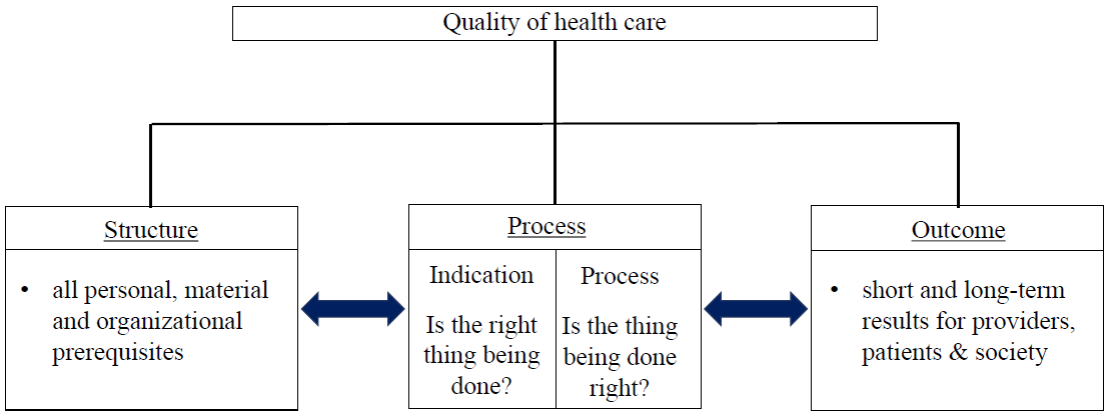


Figure 5: Categories of Quality according to Donabedian.

Source: Own figure based on Busse et al. [31] & Fleßa [32].

2.1.3.2. Quality measurement

All the concepts introduced above, such as overuse, underuse, misuse, and low-value care, can only be evaluated in terms of needs-based health care [31, 38, 40, 44]. According to the question of indication quality, i.e. whether the right thing is being done, the right thing must be defined beforehand.

For this purpose, defined clinical pathways, decision-making aids, or guidelines can be used, with the help of which attempts are already being made to influence process quality in advance [31]. Guidelines play the most important role in this context. They have systematically developed statements and recommendations that reflect the current state of knowledge and facilitate the decision-making process for treating physicians and their patients for the appropriate treatment of specific disease situations, reflect the needs-based reference care and are thus a source of information for health care providers, patients and also payers [31].

Based on this, two main approaches to measuring overuse have emerged. Overuse can be measured directly in a population and indirectly between regions [38, 45, 46]. While direct measurement allows for identifying patient or population characteristics, indirect measurement can, for example, identify unexpected variations in utilization and draw conclusions about health care organizations or structures that promote overuse [38].

2.2. Dementia

The following section provides the basic information on the clinical picture of dementia, including aetiology, epidemiology, and diagnosis and treatment.

2.2.1. Aetiology

The 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) [47] published by the WHO defines dementia in the "German Modification" [48] as a syndrome resulting from a mostly chronic or progressive disease of the brain with disturbance of many higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning ability, language, and judgment. For Förstel and Lang [49], following the ICD-10 definition, dementia is a severe loss of mental capacity due to marked long-term brain dysfunction.

Both primary and secondary dementias can be distinguished. The former includes dementia diseases whose origin is the brain. On the other hand, secondary dementias are consequences of diseases affecting other physical regions [50].

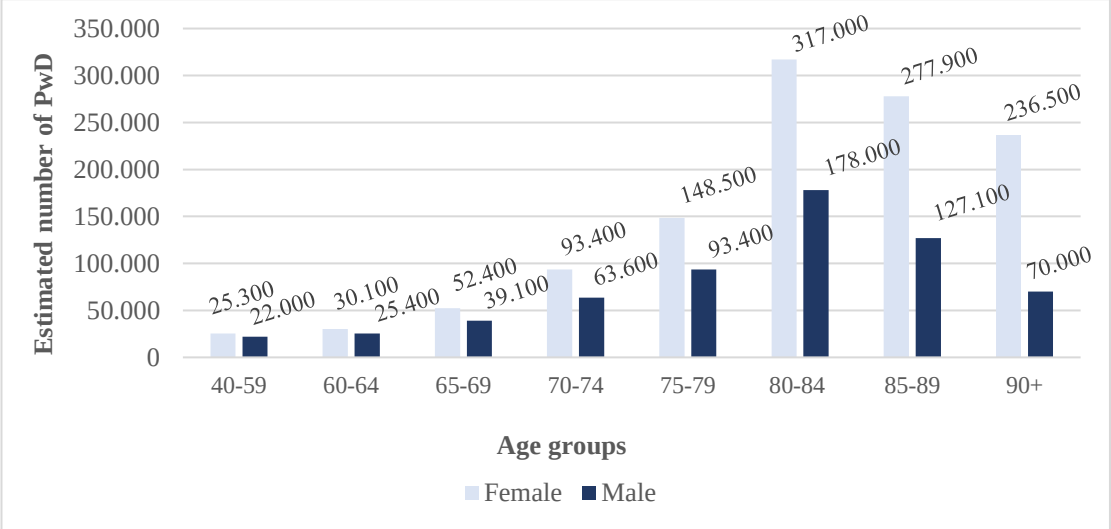
The most relevant forms of dementia include *Alzheimer's disease*. It is symptomatic of memory impairment. It is characterized by an initially slow onset with subsequent deterioration of cognitive skills, although physical limitations do not usually occur at first [51]. The second form to be mentioned at this point is *vascular dementia*. In addition to memory impairment, speech and motor skills may be impaired. Signs of a stroke may also occur [51]. Another relevant form of dementia is *frontotemporal dementia*. It is usually characterized by a personality change occurring at the beginning of the disease. This change can manifest in indifference, increasing lack of empathy or listlessness [51]. The fourth and last relevant dementia is the so-called *Lewy body dementia*. Memory impairment in this form of dementia is supplemented by symptoms that are more commonly attributed to Parkinson's disease. These include stiff muscles and trembling hands. Furthermore, affected individuals may hallucinate [51].

2.2.2. Epidemiology

In the following, a population-based view of dementia will be taken. The classic epidemiological indicators of prevalence and incidence are of particular importance. The former indicates the number of disease cases in the population, and the latter the number of new cases within a certain period. In addition, this section provides information on the duration of the disease and the expected developments in disease numbers and risk factors.

In 2019, the number of PwD was already around 57 million worldwide [52]. This number could be estimated to increase to 153 million in less than 30 years [52]. According to the WHO, Europe has the highest prevalence rate of 8.46% in persons over 65 years of age [53]. According to the latest figures, the estimated prevalence in Germany is 1.8 million PwD [14].

Further insights into dementia in Germany are provided by a breakdown of prevalence into gender, form of dementia and age group. Here it is noticeable that women are more frequently affected by dementia than men (34% vs 66%) [14]. The most common cause of dementia is Alzheimer's disease [14, 50, 51]. Dementia is age-associated, as illustrated by the following figures. While the proportion of PwD in the 65-69 age cohort is 1.9%, it is 36% in the over-90 age group [14]. Figure 6 represents the prevalence of PwD in Germany.



Abbreviations: PwD, Persons with dementia

Figure 6: Estimated prevalence of patients living with dementia in Germany in 2021

Source: Own figure based on Blotenberg & Thyrian [14].

The age-related increase is also confirmed when looking at the incidence. The incidence in 2021 is estimated to be 26 new cases of dementia per 1,000 persons aged 65 to 69 years and 104 new cases of dementia per 1,000 persons over 90 years [14]. The incidence for all persons over 65 is 436,800 in total. Given this development, disease numbers are estimated to reach 2.8 million PwD by 2050, assuming no innovations in disease prevention, diagnosis, and treatment [14].

The previous figures show that age is the most relevant factor affecting disease risk. In addition, increasing age influences the disease's duration or, more specifically, survival time. Here it can be seen that a later onset of the disease leads to a shorter duration and that dementias have a life-shortening effect and eventually lead to death. The median survival time of PwD between 65 and 75 is 6 to 8 years, but only three years for persons over 85 years [14]. Furthermore, hearing loss, smoking, depression, social isolation and many more comprise up to 40% of known modifiable risk factors for dementia [54].

2.2.3. Diagnosis and treatment

Whether it is a question of legal access to health services or the treatment process, the diagnostic or diagnosis always forms the starting point. General practitioners (GPs) usually make the diagnosis. From a health-economic point of view, it can be said that there is no demand without a diagnosis because potential patients may have an objectively detectable deficiency of which they are unaware [32]. This lack of awareness may be particularly true in the case of PwD. Thus, dementia only becomes a need for cure and thus a demand for health care services when the physician diagnoses the condition.

According to Förstel and Lang [49], the ICD-10 diagnostic criteria are decisive for the following six characteristics which must be fulfilled for a dementia diagnosis:

1. It must be a memory disorder.
2. The additional cognitive impairment must be present.
3. Sensation, as well as social behaviour, must be disturbed.

4. The threshold for mild cognitive impairment must be exceeded, which is the case if the severity of the conditions mentioned above restricts the everyday competence of the affected PwD.
5. Furthermore, the condition must have been present for at least six months.
6. Dementia must not be excluded from other causes of confusional states, such as depression or schizophrenia.

The different forms of dementia can be assigned to different degrees of severity according to the progression. The degrees of severity include both the aspect of memory impairment and the associated cognitive performance and everyday competence [49]. The presence and approximate severity of dementia can be determined with short cognitive tests such as the Mini-Mental Status Examination [55, 56].

In the case of *mild dementia*, the ability to learn new things is usually reduced, and independent living is still possible, but activities of increasing complexity can usually no longer be performed [49].

Moderate dementia includes persons who can only recall internalized and familiar information [49]. Newer information, on the other hand, is retained only temporarily and can only be reproduced for a short time [49]. Independence is reduced, and only simple household tasks are feasible, so independent living is only possible in a severely impaired form [49].

The highest degree is *severe dementia*. Persons in this stage have a highly reduced memory capacity [49]. Internalized activity and normal behaviour can only be recalled in fragments [49]. The absorption of new knowledge or information and finding one's way in everyday life is no longer possible due to the lost cognitive abilities [49].

If the differentiation from other symptom patterns and diseases has been made and a dementia diagnosis, including severity, is available, a differential diagnosis should also be made to differentiate dementia aetiologically [50, 51, 55]. For this purpose, GPs usually cooperate with specialists in the context of differential diagnosis. Only with sufficient information can patients and their relatives be optimally advised and educated to draw up an individual treatment plan [51].

From the individual's perspective, the aim is to maintain self-determination, independence and thus a high quality of life and social participation, as well as to live as long as possible in familiar surroundings [57]. From this, needs can be derived, which must be considered in the medical, nursing and social dimensions of dementia care, underlining the need for interdisciplinary approaches [57].

Medical care distinguishes between non-drug and drug therapies. Drug therapies address the core symptoms of dementia per se and, if necessary, treat psychological and behavioural symptoms [55]. The most important antidementia drugs currently approved in Germany for treating core symptoms are acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) and memantine. Furthermore, PwD have an increased risk of suffering from various comorbidities that cause numerous symptoms and require additional treatments [58].

Non-drug therapies include psychosocial interventions such as occupational therapy [55]. Primary care physicians and specialists usually prescribe or initiate medical care services. Other crucial components that complete dementia care include nursing and medical care in outpatient, day-care, and inpatient structures, where these complementary non-drug therapies, such as occupational therapy and psychotherapy, are ultimately offered and delivered [59].

About 75% of PwD are assumed to live in their social environment and familiar surroundings [16, 57]. Another relevant aspect affecting PwD care is the so-called informal care based on the support provided by family members or other persons from the social structure (circle of acquaintances) of the person concerned [59].

2.3. Dementia-related patient-reported outcomes

In the following, the relevance of health-related quality of life (HRQoL), hospitalizations, and medical costs as the main outcome dimensions for this work will be elaborated.

2.3.1. Health-related quality of life

When considering the effects of health care services, a distinction is first made between intangible and tangible effects. Intangible effects are not naturally present in monetary form, whereas tangible effects can be measured in monetary terms [60]. Thus, the effects of utility services on patients' quality of life are among the intangibles.

The growing health economic importance of quality of life originates in the epidemiological transition [12, 32]. Chronic diseases with no prospect of cure are on the rise. Furthermore, there is an awareness of concomitant diseases that do not affect the lifespan but do affect well-being [60], which is also true for the chronic degenerative clinical picture of dementia; therefore, the stabilization of quality of life is one of the most important therapeutic goals in the care of PwD [57, 61].

HRQoL is based on the definition or, more specifically, the concept of health provided by the WHO (2.1.1.1). Thus the distinction between mental, physical and social health must also be reflected in the respective measurement instruments.

A distinction is made between profile and index instruments. While profile instruments determine values for each dimension of quality of life, index instruments combine individual dimensions into a single measure [60]. Furthermore, the instruments can be differentiated according to their disease-relatedness. There are both disease-specific and cross-disease (generic) instruments [60]. For example, the Quality of Life in Alzheimer's Disease [62] is a disease-specific index instrument, whereas the 12-item Short-Form Health Survey [63] is a generic profile instrument.

The main challenges affecting the HRQoL-assessment in PwD are, depending on dementia severity, the decline in cognitive functions and the impaired perception of time, limiting capacities in attention, judgment, and communication depending on dementia severity. Therefore, it is common to rely on proxy ratings by, for example, family members and informal caregivers instead of self-assessments as the severity of dementia increases.

2.3.2. Hospitalizations in dementia

Although hospitalizations can generally be analyzed through the lens of health care utilization, the material differences between, for example, a GP visit and a hospital admission are insufficiently addressed in the course of those analyses. While the primary care physician is indispensable for optimal care as part of his gatekeeper function and tends to bring about positive outcomes, hospitalizations always have negative implications for HRQoL, especially for PwD.

Hospitalizations lead to adverse outcomes for PwD, such as the increased risk of institutionalization or increased mortality [64]. Favouring factors in this regard are dementia severity, number of medications, and deficits in activities of daily living [64].

PwD generally have a higher risk of hospitalization than persons who do not have dementia [65, 66]. The reasons for this are not so much dementia as the primary diagnosis but are multifaceted [67]. For example, dementia patients are often admitted as emergencies due to infections, fractures or nutritional disorders for which they are then treated in a hospital [65, 66, 68].

Other studies show that PwD in acute care hospitals are older, require more hours of care, stay longer in the hospital, and are at higher risk for delayed discharge and loss of function during admission, resulting in more hospital resources being tied up and higher costs [68, 69].

2.3.3. Resource utilization and health care costs in dementia

Costs as outcomes play the determining role in health economic analyses. The differentiation of cost types is based on the following questions: i) To whom or what can the costs be attributed? and ii) Are the costs measurable in monetary units?

The categorization of direct and indirect costs follows the question of attribution. Direct costs comprise the monetarily valued medical and non-medical use of resources for complete health care services [70]. On the other hand, indirect costs are understood

to be negative external effects, e.g. economic productivity losses due to a loss of potential labour [70].

The second question entails the division into tangible and intangible costs, as mentioned within the HRQoL-section. Tangible costs can be valued in monetary units and thus follow a classical understanding of the concept of cos ts [70]. In contrast, intangible costs such as pain or quality of life cannot be valued monetarily or only to a limited extent [60, 70]. Particularly in the case of chronic diseases with no prospect of cure, such as dementia, the assessment of service needs to examine the intangible effects to evaluate the benefit of an intervention.

In general, the attribution of costs depends on the perspective taken. They can be calculated from the aggregated societal perspective or the perspective of the health care providers, the health insurers, and the patients [70].

Cost is usually determined in the following three steps: i) first, the relevant cost components are identified, ii) then, the resource consumption is measured, and iii) finally, the monetary valuation of the resource units is performed [70].

In the following, a brief overview of the disease costs of dementia will be presented. The cost of dementia worldwide was estimated to exceed $1 trillion in 2018 and could double by the end of this decade [71, 72]. The highest economic burden was found in the high-income regions of Europe and North America [71, 72].

The German Federal Statistical Office [73] estimates total disease costs in Germany for 2020 at €431.8 billion. €221.8 billion (51%) of this amount is incurred by the over-65 age group [73]. The share of disease costs for dementia amounts to €20.4 billion (5%), after an increase of approximately 32% (+€5.0 billion) between 2015 and 2020 [15]. In the same period, total disease costs increased by only 28% (+€93.4 billion) [15, 73]. Figure 5 summarizes this outlined development of disease costs in Germany.

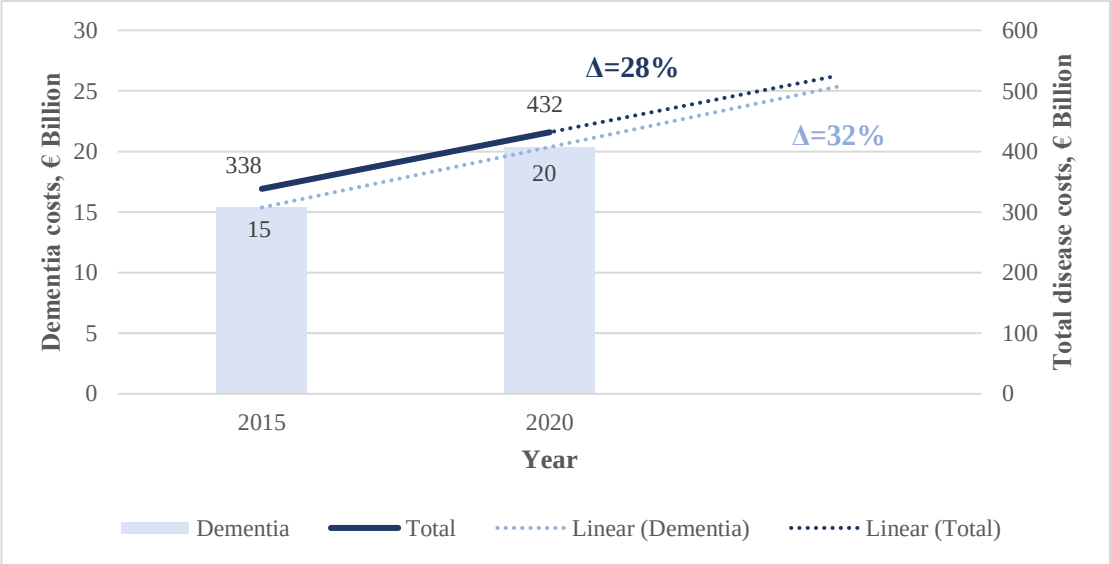


Figure 7: Disease costs in Germany between 2015 and 2020.

Source: Own figure based on the German Federal Statistical Office [72].

In a meta-analysis, Michalowsky et al. [16] estimate the costs for PwD from the payers' perspective to be €34 billion in 2016, which could increase to €90 billion by 2060. Excess costs of dementia for payers accounted for 11% of total costs for persons aged 65 and older in 2016 and are projected to increase to 15% by 2060 [16]. According to this study, similar development can be observed for the costs for society as a whole (plus the costs of informal care), estimated at €73 billion in 2016 and €195 billion by 2060 [16]. Per patient with dementia, this corresponds to €20,658 for payers and €44,659 for society as a whole [16]. Compared to patients without dementia, additional costs per patient with dementia are estimated to be €11,205 for payers and €33,188 from the perspective of society as a whole [16].

While medical care costs decrease with dementia progression and increasing age, nursing care costs double with increasing dementia severity [19]. However, care costs increase again with increasing proximity to death [74]. The main cost driver across all cost categories is the functional impairment of affected PwD [19, 75, 76].

2.4. Low-value care in dementia and affected outcomes

This section summarizes the international and national evidence base on general low-value care, especially Lvm. It also maps the existing literature on low-value dementia care. Finally, research gaps will be identified, and the key research questions examined here will be derived.

2.4.1. International and national studies

Morgan et al. [77] published a research agenda for medical overuse for the first time in 2015, as research on the impact of overuse and low-value care had been rather uncoordinated and lacked consistent terminology up to that point. At its core, the agenda provides for the following steps: i) measuring frequencies, ii) identifying factors that promote overuse and low-value care, iii) measuring impact, and finally, iv) developing and implementing strategies to curb low-value care and overuse [77]. The study evidence can also be appropriately categorized, building on these steps.

The majority of studies focus on measuring the prevalence of low-value services. Low-value health services are common, and prevalence has decreased slightly in recent years [78]. The prevalence varies between indications and services but also between providers. Müskens et al. [79] studied low-value pharmaceutical care among Dutch primary care physicians and found that prevalence varied between 3% and 88% depending on the indication. Concerning dementia care, the pharmaceutical supply of antipsychotics is a particular problem [80]. In an Australian study, Brett et al. [28] found little change in the frequency of antipsychotic prescribing in PwD over three years (2013-2016).

In contrast, some studies are devoted to factors that promote the provision of low-value services. Walter et al. [81] conducted semi-structured interviews with primary care physicians from the U.S. to identify reasons for low-value prescribing, describing the causes of low-value prescribing as multifactorial. Providers see the factors in patients, prescribers, and the health care system. Kool et al. [82] surveyed primary care physicians in the Netherlands, wherein 67% indicated that low-value treatments are regularly used due to lack of time, but also the fact that care providers want to

maintain the relationship with their patients by offering them an intervention rather than waiting. Studies by Hoffmann et al. [83, 84] showed that distorted perceptions, beliefs, and expectations play an important role among both patients and clinicians, which tend to overestimate the benefits of the intervention and underestimate the potential harms. Verkerk et al. [85] also conducted semi-structured interviews in the U.S., Canada, and the Netherlands and pointed to the reimbursement system, industry influence, and fear of malpractice litigation as factors favouring low-value care.

Korenstein et al. [86, 87] criticize that most research has focused on the prevalence of overuse and its causes. Regarding the goal of eventually reducing low-value care, the authors emphasize that presenting the problem using the spectrum of potential harms is more effective. To this end, they have identified six negative consequences for patients: physical, psychological, social, and financial burden, treatment burden, and dissatisfaction with health care [86, 87]. However, most studies published to date are mostly based on claims data rather than primary data, which does not consider the personal effects at the patient level but reflects physicians' documentation or billing behaviour. Therefore, especially the tangible financial consequences are well-studied [25]. A recently published study from France confirmed an association between inappropriate prescribing and health care costs [26]. In addition, recently published U.S. studies examined the downstream effects of low-value care procedures in hospitals and found that patients who received low-value care were associated with higher Medicare costs and longer lengths of stay [88, 89]. Furthermore, evidence shows that low-value care can trigger avoidable care cascades [90]. Despite these developments, studies examining the impact of low-value care, especially on patient-reported outcomes, remain scarce. Furthermore, longitudinal studies confirming previous cross-sectional findings are still lacking.

The final category includes multifaceted approaches to developing and implementing strategies to curb low-value care and overuse, also known as de-implementation. Verkerk et al. [37] have developed a typology with three types of low-value care, each of which entails different strategies for reducing low-value care. They distinguish ineffective care, which needs to be *limited*; inefficient care, which needs to be *leaned* organizationally; and unwanted care, which is about patient preferences and needs to be *listened* to [37]. Norton and Chambers [91] cite four action measures under the

umbrella term de-implementation: the *removal*, *replacement*, *reduction*, or *restriction* of an inappropriate intervention. The points of reference are not so much the perspectives of the respective stakeholders or levels of action, as in Verkerk et al. [37], but health care services or treatments that require different actions depending on whether it is a drug or a screening test, for instance.

According to Raudasoja et al. [92], most studies on the de-implementation of low-value care services examined only one specific service, including most frequently the prescription of medication, an imaging procedure, or screening, the majority in primary care or hospital settings with the participation of providers, patients, or both. Critically, Maratt et al. [93] highlight that most publications focus only on reducing utilization than considering clinically relevant patient-level outcomes. Regularly, interventions targeting de-implementation can start with the provider or the patient, for example, through decision support or information materials to increase patient sovereignty and thus enable shared decision-making [4, 94-96]. In particular, according to a systematic review by Sypes et al. [96], patient empowerment can demonstrate practical effects. However, expectations in this regard should be tempered concerning the care of PwD, depending on severity. All in all, there is still no single model for de-implementation, as the frameworks of individual health systems differ and are always context-specific [97, 98].

In Germany, research on overuse and low-value care lags behind and lacks uniform terminology. However, efforts to change this are discernible, although they are largely pushed by medical societies, as the guiding theme "Weniger ist mehr" (Less is more) of the annual meeting of the German Society of Internal Medicine (DGIM) 2021 shows [99, 100]. A few years ago, the DGIM took up the "Choosing wisely" initiative launched by the American Board of Internal Medicine in 2011, added the topic of underuse, and published the German counterpart under the title "Klug entscheiden" (Choosing wisely) [100, 101]. Without referring to an indication, close to 70% of DGIM members reported being confronted with overuse several times a week [101]. However, the German state of research cannot be adequately represented under a consistent term such as overuse. The research approaches are each limited to the prevalence of individual aspects of care, such as imaging procedures for back pain or inappropriate prescribing [43].

The latter includes, in particular, potentially inappropriate medication (PIM) in aged persons. In 2010, Holt et al. [102] published the so-called PRISCUS list, which lists potentially inappropriate drugs for elderly patients and their therapy alternatives. An update was made in 2023 [103]. In the meantime, other PIM lists such as EU(7) PIM [104] or Fit fOR The Aged (FORTA) [105] have been published. Although the problem has been known for some time, several studies that included physician-centred education or shared decision-making tools reported that they partially reduced polypharmacy but did not affect clinically relevant outcomes such as hospitalizations, HRQoL and mortality [106-108]. In a cross-sectional study published in 2021 (more than ten years after the publication of the PRISCUS list), a comparison of the three PIM classifications showed prevalences of 56% for the FORTA classification, 25% for the PRISCUS list, and 70% for the EU(7) PIM list in primary care in Germany [109].

The provision or use of low-value care, particularly the overuse of potentially inappropriate medications for chronic, age-related conditions such as dementia, is common. The prevalence of PIM in PwD varies widely depending on the tool used and the setting studied. Renom-Guiteras et al. [110], in a Europe-wide study, report a PIM prevalence of 62% according to the EU(7) PIM list for PwD in long-term inpatient and outpatient care, whereas Wucherer et al. [27] report the prevalence of PIM in PwD in primary care as 22% according to the PRSICUS list.

2.4.2. Research gaps

PwD are a vulnerable, multimorbid population that needs high-value care to delay the progression of cognitive decline, increase or maintain HRQoL and live community-dwelling as long as possible [111-113]. However, studies have shown that PwD rarely receive evidence-based treatment and care according to guidelines [114]. Only 39% of people with positive dementia screening in primary care received a formal diagnosis at all [115], only 30% of PwD received antidementia medication [19, 20, 116], and 36% received nondrug therapies as recommended in guidelines [21]. In addition to the presence of multiple coexisting conditions (multimorbidity), most dementia patients also receive multiple medications (polypharmacy), which increases the risk for low-

value care [58, 117, 118]. Drug-related problems have also been identified in 93% of PwD, associated with increased health care costs [22, 119].

As described in 2.4.1, the still high prevalence of Lvm, especially in PIM, has also been adequately studied for the German health care system. International research also significantly contributes to the conditions and factors that promote or favour the provision of low-value care in general and Lvm in particular. The reasons are usually multifactorial and include systemic and patient- and provider-related factors. However, the findings cannot simply be transferred to the German health care system, especially because of the system- and provider-related factors.

Furthermore, there is a lack of coherent research that considers patient-relevant outcomes in the context of overuse and low-value care and thus adequately reflects harm at the patient level, as most studies rely on claims data. These could be reasons for the assumption by Maratt et al. [93] that despite de-implementation strategies reducing the utilization of e.g. medications, they achieved no measurable improvements for patients because clinically relevant patient-level outcomes are not considered, as was finally the case in Rieckert et al. [106], Rudolf et al. [107] or Schäfer et al. [108].

Ultimately, most of the literature is based on cross-sectional studies, and longitudinal effects of low-value care on patient-relevant outcomes are rarely reported.

Therefore, the objectives of the present study are:

1. To determine the prevalence of PwD who received low-value medications and describe the change in prevalence over 24 months,
2. To identify the associations between low-value medications and patient-reported and health economic outcomes such as health-related quality of life, hospitalizations, and direct medical care costs among community-dwelling persons living with dementia, and
3. To demonstrate the impact of low-value medications on health-related quality of life, hospitalizations, and direct medical care costs in dementia longitudinaly over 24 months.

3. Methods

The following section outlines the study design and participant flow of the DelpHi-MV trial from which the data were drawn. Data collection is described below, with additional questions on how and what data were assessed, including socio-demographic and clinical characteristics, Lvm measurement, HRQoL, resource utilization and health care costs. Finally, the statistical analysis methods used are explained in more detail.

3.1. Study design, setting and participant flow of the DelpHi-MV trial

Both cross-sectional and longitudinal analyses were based on data from the DelpHi-cohort extracted from the cluster-randomized, controlled interventional DelpHi-MV trial (Dementia: life- and person-centred Help in Mecklenburg-Western Pomerania) [30]. In their practices, 125 GPs screened 6,838 patients systematically for possible cognitive impairment or dementia, respectively, using the short interview-based DemTect screening procedure [120] if patients were considered potentially suitable for participation. A total of 1,166 (17%) patients met the following eligibility criteria:

1. DemTect <9,
2. ≥70 years old and
3. living at home.

They were informed about the study by their respective GP and were asked to provide written informed consent and, if possible, to name a caregiver. The consent forms were previously approved by the responsible Ethical Committee of the Chamber of Physicians of Mecklenburg-Western Pomerania under the registry number BB 20/11. Finally, 634 eligible patients (54%) provided the required informed consent. The detailed design has been described in the study protocol [30].

The enrolment and data collection for the baseline assessment began on 1 January 2012 and ended on 31 December 2014. The second follow-up period ended on March 2017. The baseline assessment was started by 516 PwD, constituting the basis for the cross-sectional analyses. Regarding longitudinal analyses, comprehensive data assessments at baseline and after 12 and 24 months were completed by 352 PwD.

Patients who dropped out of the study had a significantly higher functional impairment (odds ratio (OR) 1.10; 95% confidence interval (CI), 1.01 – 1.19). The drop-out analysis is shown in Table 1. Additional analyses examining the drop-out reason by death revealed no significant differences in the distribution of mortality between those with and without Lvm and no effect of Lvm on drop-out by death (see Supplementary Tables 1, 2 and Supplementary Figure 1). The detailed participant flow is displayed in Figure 8.

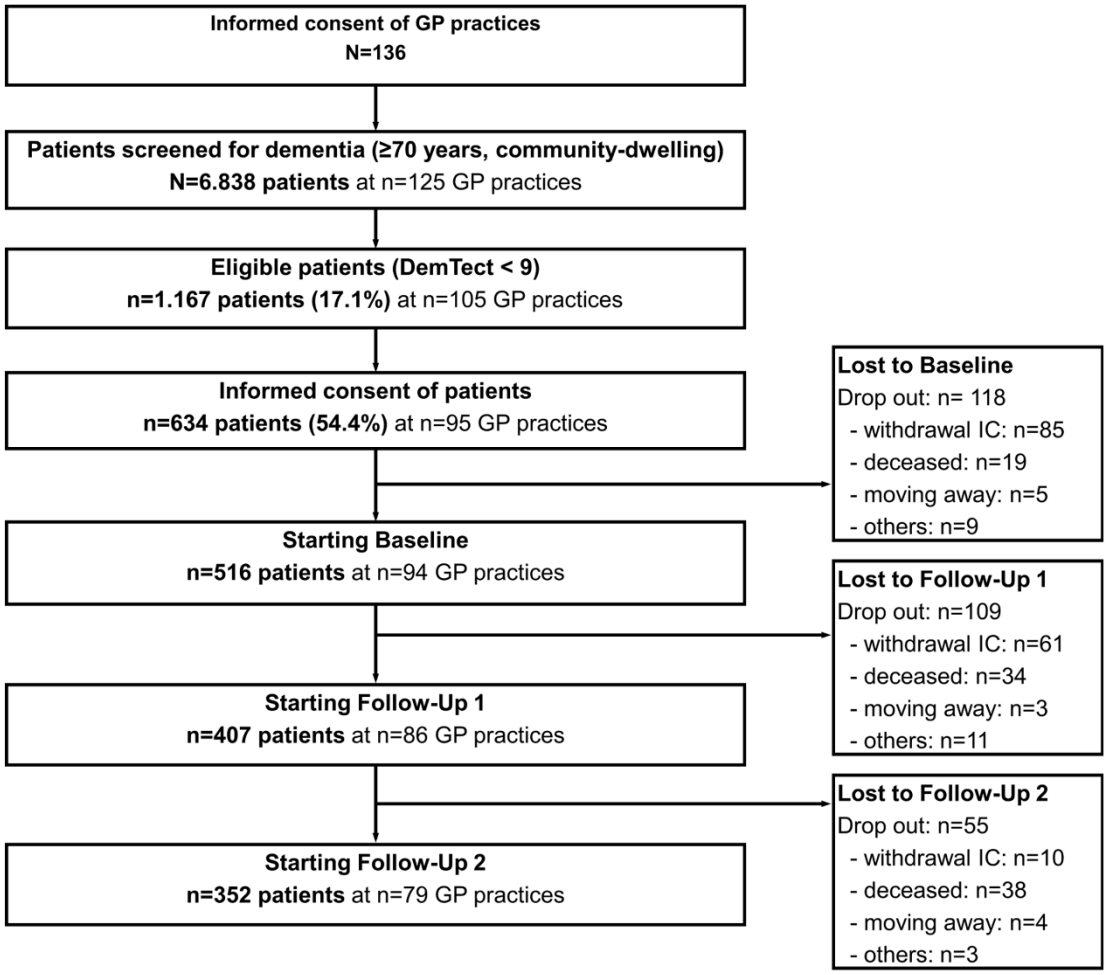


Figure 8: Study flowchart

Source: Own figure.

Table 1: Drop-out-analyses for patients who dropped out before baseline and after completing the baseline assessment

Lost to baseline, of n=634	**Withdrawal of IC (n=99, 15.6%)**			**Death (n=19, 2.9%)**			**Drop-out overall (n=118, 18.6%)**		
	OR	**95% CI**	***p value***	**OR**	**95% CI**	***p value***	**OR**	**95% CI**	***p value***
Age	1.01	0.97 – 1.05	0.506	0.95	0.97 – 1.04	0.325	1.00	0.96 – 1.04	0.827
Sex (Ref. female)	0.84	0.52 – 1.37	0.495	1.30	0.49 – 3.4	0.593	0.89	0.57 – 1.38	0.608
DemTect Score	0.93	0.83 – 1.04	0.251	0.88	0.72 – 1.08	0.230	0.92	0.83 – 1.01	0.113
Lost after baseline, of n=516	**Withdrawal of IC and other reasons (n=92, 17.8%)**			**Death (n=72, 14.0%)**			**Drop-out overall (n=164, 31.8%)**		
	OR	**95% CI**	***p value***	**OR**	**95% CI**	***p value***	**OR**	**95% CI**	***p value***
Age	1.00	0.95 – 1.04	0.876	1.04	1.00 – 1.09	0.078	1.02	0.99 – 1.06	0.240
Sex (Ref. female)	0.84	0.52 – 1.36	0.480	0.83	0.50 – 1.37	0.463	0.78	0.52 – 1.16	0.226
Living situation (Ref. alone)	0.98	0.60 – 1.58	0.927	1.06	0.64 – 1.76	0.817	1.76	0.68 – 1.50	0.972
Comorbidity (ICD-10 Diagnoses)	0.96	0.86 – 1.07	0.473	1.02	0.91 – 1.13	0.751	0.98	0.90 – 1.08	0.734
Cognitive impairment (MMSE)	1.03	0.98 – 1.09	0.236	**0.93**	**0.89 – 0.98**	**0.002**	0.97	0.93 – 1.01	0.131
Depression (GDS)	0.93	0.84 – 1.04	0.194	**1.16**	**1.05 – 1.28**	**0.003**	1.05	0.97 – 1.14	0.224
Activities in daily living (BADL)	0.91	0.82 – 1.00	0.060	**1.26**	**1.15 – 1.39**	**<0.001**	**1.10**	**1.01 – 1.19**	**0.021**

Abbreviations: *IC* informed consent; *MMSE* Mini-Mental State Examination, Range 0-30, higher score indicates better cognitive function; *B-ADL* Bayer-Activities of Daily Living Scale, range 0-10, lower score indicates better performance; *GDS* Geriatric Depression Scale, sum score 0-15, score ≥ 6 indicates depression; *ICD* International Statistical Classification of Diseases and Related Health Problems, *OR* odds ratios; *Ref*, reference; *CI* confidence interval
Univariate logistic regression analysis with random effects for the general practitioner
Values in bold indicate $p < 0.05$

3.2. Data collection

3.2.1. Sociodemographic and clinical variables

Within the DelpHi-MV trial, dementia-specific qualified nurses conducted comprehensive, standardized, computer-assisted interviews in the participants' homes at baseline and 12 and 24 months after baseline to assess sociodemographic data (age, sex, living situation) and the following clinical variables:

- *Cognitive impairment*, according to the Mini-Mental State Examination (MMSE) [56], ranges from 0 to 30, whereas a higher score indicates better cognitive function;
- *Deficits in daily living activities*, according to the Bayer Activities of Daily Living Scale (B-ADL) [121], ranges from 0 to 10, whereas a lower score indicates better performance;
- *Depression symptoms*, according to the Geriatric Depression Scale (GDS) [122], comprise a sum score from 0 to 15, whereas a score ≥ 6 indicates depression; and
- *Comorbidities* according to the number of ICD-10 [47] diagnoses listed in the GP files, complemented by the Charlson comorbidity index (CCI) [123].

3.2.2. Low-value medication measurement

Medication data were captured within a standardized home medication review to assess all regularly taken drugs, including over-the-counter and prescribed medications, providing a more comprehensive picture of patients' Lvm use beyond documented prescriptions from physicians [30, 116, 124]. The medications recorded were validated with medication lists provided by the treating GP or, if available, by the administering nursing service.

These three sources were used as references for classifying Lvm in dementia [125-127]: 1) the German "S3 guideline: Dementia" published by the German Association for Psychiatry, Psychotherapy and Psychosomatics and the German Society for Neurology [55], which lists selected medications that are ineffective and should be

avoided, 2) the PRISCUS list [102], including a total of 83 substances of 18 drug classes that are potentially inappropriate for elderly individuals; and 3) recommendations for avoiding harmful treatments of the German counterpart of the international "Choosing Wisely" campaign [101]. Three reviewers selected the Lvm-related recommendations according to the following criteria [125-127]:

1. relevance;
2. targeted audience;
3. differentiation criteria for inappropriateness, and
4. evaluability in the dataset used for the present analysis.

Thirty-nine active substances were identified and assigned to 10 measurable Lvm treatments. Lvm variables were categorized as follows:

1. *Dichotomously* (receiving Lvm vs. not receiving Lvm (within 24 months)) and
2. Additionally, for the longitudinal analyses as a *time referencing variable*, considering the intensity of Lvm intake as a cumulative effect:
   2.1. receiving Lvm at only one out of the three data assessments (sporadic);
   2.2. over one year – from baseline to 12-month follow-up or from 12 to 24 months of follow-up; or
   2.3. continuously over two years – from baseline to 24 months of follow-up.

Table 2 demonstrates all Lvm used within this analysis for the longitudinal sample.

3.2.3. Health-related quality of life

The HRQoL-assessment was integrated into the mentioned comprehensive, standardized, computer-assisted interviews conducted at baseline and 12 and 24 months after baseline. HRQoL was assessed using the disease-specific index instrument Quality of Life-AD (QoL-AD) [62] and the generic profile instrument 12-Item Short-Form Health Survey (SF-12), the short form of the SF-36 [63]. The dementia-specific QoL-AD is the most commonly used health-related quality-of-life questionnaire in dementia with good psychometric properties [62, 125]. The QoL-AD includes 13 items with a four-point Likert scale. The total score ranges between 13 and 52, indicating very low and high HRQoL, respectively [62, 125].

Table 2: Ten Low-value medication treatments: active substances included, data requirements, and counts

Lvm by active substance class [59, 105, 106]	Active substance (further condition)	Data requierements[†]	PwD receiving LVM		
			at baseline n=126, n (%)	after 12 mo n=120, n (%)	after 24 mo n=102, n (%)
Low-value antiphlogistics/ analgesics	Dexketoprofen	ATC (M01AE17)	43 (34.1)	41 (34.2)	32 (31.4)
	Etoricoxib	ATC (M01AH05)			
	Indometacin	ATC (M02AA23, M01AB01)			
	Meloxicam	ATC (M01AC06)			
	Naproxen	ATC (M01AE02)			
	Diclofenac	ATC (M01AB05, M02AA15)			
Low-value antidementia drug treatments	Memantine (guideline recommendation for mild dementia)	ATC (N06DX01) MMSE (≥20)	32 (25.3)	37 (30.8)	6 (5.9)
	Naftidrofuryl	ATC (C04AX21)			
	Piracetam	ATC (N06BX03)			
	Dihydroergotoxine	ATC (N06DX07)			
Low-value sedatives/ hypnotics	Chloral hydrate	ATC (N05CC01)	22 (17.5)	22 (18.3)	18 (17.6)
	Chlordiazepoxide	ATC (N05BA02)			
	Clobazam	ATC (N05BA09)			
	Diazepam	ATC (N05BA01)			
	Zopiclon	ATC (N05CF01)			
	Diphenhydramine	ATC (N05CM20)			
	Doxylamine	ATC (N05CM21)			
	Medazepam	ATC (N05BA03)			

Continued Table 2: Ten Low-value medication treatments: active substances included, data requirements, and counts

Lvm by active substance class [59, 105, 106]	Active substance (further condition)	Data requierements†	PwD receiving LVM at baseline n=126, n (%)	after 12 mo n=120, n (%)	after 24 mo n=102, n (%)
(Cont.) Low-value sedatives/ hypnotics	Nitrazepam	ATC (N05CD02)			
	Zolpidem	ATC (N05CF02)			
Low-value antidepressants	Amitriptyline	ATC (N06AA09)	17 (13.5)	13 (10.8)	10 (9.8)
	Amitriptylinoxide	ATC (N06AA25)			
	Doxepin	ATC (N06AA12)			
	Trimipramine	ATC (N06AA06)			
Low-value antipsychotics	Levomepromazine	ATC (N05AA02)	13 (10.3)	16 (13.3)	19 (18.6)
	Olanzapine	ATC (N05AH03)			
	Haloperidol	ATC (N05AD01)			
	Quetiapin (guideline recommendation for agitation and aggression)	ATC (N05AH04) NPI‡ (≥1)			
Low-value antihypertensives	Clonidine	ATC (S01EA04, C02AC01)	12 (9.5)	9 (7.5)	8 (7.8)
	Doxazosin	ATC (C02CA04)			
	Methyldopa	ATC (C02AB01)			
Low-value spasmolytics	Solifenacin	ATC (G04BD08)	7 (5.6)	5 (4.2)	6 (5.9)
	Tolterodine	ATC (G04BD07)			
Low-value antiarrhythmics	Acetyldigoxin	ATC (C01AA02)	4 (3.2)	4 (3.3)	2 (2.0)
	Flecainide	ATC (C01BC04)			
	Sotalol	ATC (C07AA07)			
Low-value muscle relaxants	Baclofen	ATC (M03BX01)	2 (1.6)	2 (1.6)	1 (1.0)
	Tetrazepam	ATC (M03BX07)			
Low-value antiemetics	Dimenhydrinate	ATC (A04AB02)	1 (0.8)	-	-

Abbreviations: ATC Anatomical Therapeutic Chemical; Cont. continued; Lvm Low-value medications; MMSE Mini-Mental State Examination, range 0-30, higher score indicates better cognitive function; mo, months; NPI Neuropsychiatric Inventory, score ≥ 5 indicates clinically relevant symptoms; PwD Persons with Dementia †beyond demographic data (e.g. age) ‡Score for agitation and aggression

On a range between 0 and 100, the SF-12 measures both physical dimensions (SF-12-PCS), including the perception of general health; physical functioning, bodily pain, and role limitations due to the physical health state; and mental dimensions (SF-12-MSC), comprising social functioning, mental health, vitality and role limitations due to the emotional state [63]. A higher score indicates better quality of life. Moreover, the SF-12 is valid as a health status instrument in large community-based studies of older people and suitable for mildly to moderately cognitively impaired PwD [128, 129].

3.2.4. Resource utilization and health care costs

The health care costs were determined by the three steps explained above in section 2.3.3. First, the relevant cost components were identified, then the health resource utilization was measured, and finally, the resource use was monetarily evaluated. The present analyses calculated direct medical care costs from the payers' perspective, whereas formal and informal care and indirect costs, such as lost productivity, were not considered.

For the second step, a health resource utilization review was conducted at baseline and 12 and 24 months after baseline to record the utilization data retrospectively for the last 12 months each. The dementia-specific qualified nurses query a list of common health resources and services to the PwD to avoid possible recall biases. In addition, participants' caregivers assisted if present in the interview and were asked to complete the questionnaire to validate the patient's data and improve precision and data quality. Moreover, other available proxies, such as executing nursing services, were consulted in case of missing data.

The health resource utilization assessment captured detailed information about the frequency (number of visits, days stayed or quantities) of medical service utilization: physician consultations (GP, specialists), medication, aids, therapies (occupational, physical and speech therapy), and in-hospital care (acute and planned hospital admissions) [30]. Additionally, as patient-reported data and primary outcome, hospitalizations were assessed dichotomously (at least one vs. none). A bottom-up and prevalence cost of illness design was used to calculate the average costs for medical

care per PwD retrospective for one year. Health resource utilization was monetarily valued using standardized unit costs (inflated to 2020 for the cross-sectional and to 2022 for the longitudinal cost analyses; calculated in euros [€]) [130, 131].

A bottom-up and prevalence cost of illness design was used to calculate the average costs for medical care per PwD retrospective for one year. Health resource utilization was monetarily valued using standardized unit costs (inflated to 2020 for the cross-sectional and to 2022 for the longitudinal cost analyses; calculated in euros [€]) [130, 131]. Furthermore, deltas (Δ) were calculated (cost difference between baseline and one/two year(s) after baseline) to assess the change in total health care costs after 24 months. Table 3 summarizes detailed information about the monetary valuation of the services.

3.3. Statistical analysis

The prevalence of Lvm and group differences (receiving no Lvm vs at least one Lvm) in study participants' sociodemographic and clinical characteristics and patient-reported (HRQoL, hospitalizations) or health economic (health care costs) outcomes were presented using descriptive statistics. The statistical significance of group differences was determined using t-tests and one-way analysis of variance for differences in means and Fisher exact tests, and Kruskal-Wallis test for differences in proportions.

Regarding cross-sectional analyses, multiple linear regression models for each patient (*i*) were applied to assess the individual association between Lvm and HRQoL (linear regression), hospitalizations (logistic regression), and costs (linear regression). The dependent variables were $HRQoL_i$ (Qol-AD, SF-12-MCS, SF-12-PCS), $hospitalization_i$ (dichotomous: yes/no) and *total direct medical care* $costs_i$ and the following subcategories: *costs for physician* $treatments_i$, *inpatient* $treatments_i$, $medications_i$, *medical* $aids_i$, and *outpatient* $therapies_i$ [125, 126]. Lvm_i (dichotomous: no Lvm vs at least one Lvm) was used as an independent variable. Models were furthermore adjusted for the following sociodemographic and clinical factors: age_i, sex_i, $cognition_i$ (MMSE), *functional* $impairment_i$ (B-ADL), $depression_i$ (GDS), as well as $comorbidities_i$ (dichotomous: yes/no for each) according to the CCI and

Table 3: Methods and used unit costs for monetary valuation of medical care services (based on Michalowsky et al.[132])

Cost categories	Services	Units	Unit costs*	Unit cost & source for monetary valuation
Medical care				
Outpatient physician treatment	GP or specialists	Visits	21.16€ - 82.38€, depending on specialization	Cost per visit [131]
Inpatient treatment	In-hospital treatment	Days	598.97€	Average per diem cost for in-hospital treatment in Mecklenburg-Western Pomerania & for specialization of rehabilitation [130]
Medications	Regularly prescribed drugs (Rx-drugs)	Quantity	Market prices, 256.12€†	Pharmaceutical Index of the Scientific Institute of the AOK [134]
Medical aids	Aids such as tub-lifts, tub-seats, walking sticks, walkers and others	Quantity	Market prices, 170.61€†	Market prices [130]
Other outpatient treatment	Occupational therapy, speech therapy, physiotherapy and others	Visits	27.62€	Cost per contact & reimbursement schedules of statutory health insurance [133]

Abbreviations: *GP*, general practitioner; *AOK*, Allgemeine Ortskrankenkasse ∗ Inflation included. † When drugs, aids, or services were unknown or market prices were not available.

multimorbidity$_i$ (number of ICD-10 diagnoses) to consider the context in which treatments were prescribed and to minimize confounding [125, 126]. Since patients were recruited in different clusters (i.e., GP practices), patient outcomes, treatment, and care could be stochastically dependent on the GP practice [125, 126]. Therefore, we used random effects to adjust for the effects of the clusters in each of our regression models. Due to the highly skewed distribution of medical care costs, standard errors and confidence intervals were determined using nonparametric bootstrapping (2,000 replications) [125, 126, 135]. The models for linear regressions and logistic regression, respectively, are represented in formulas (1), (2) and (3).

(1) $$HRQoL_i = \beta_0 + \beta_1 * Lvm_i + \beta_2 * age_i + \beta_3 * sex_i + \beta_4 * MMSE_i + \beta_5 * B-ADL_i + \beta_6 * GDS_i + \beta_7 * comorbidities_i + \beta_8 * multimorbidity_i + \in_i$$

(2) $$P(Hospitalization)_i = \frac{1}{1+e^{-(z_i)}}$$, whereas

(2.1) $$z_i = \beta_0 + \beta_1 Lvm_i + \beta_2 age_i + \beta_3 sex_i + \beta_4 MMSE_i + \beta_5 BADL_i + \beta_6 GDS_i + \beta_7 comorbidities_i + \beta_8 multimorbidity_i + \in_i$$

(3) $$Medical\ care\ costs_i = \beta_0 + \beta_1 * Lvm_i + \beta_2 * age_i + \beta_3 * sex_i + \beta_4 * MMSE_i + \beta_5 * B-ADL_i + \beta_6 * GDS_i + \beta_7 * comorbidities_i + \beta_8 * multimorbidity_i + \in_i$$

Regarding the longitudinal analyses, multivariable panel data regression models with specifications corresponding to the scale level of the respective outcome variable were fitted to assess the effects of Lvm on patients' HRQoL (linear regression), hospitalizations (logistic regression) and costs (linear regression). Compared to the cross-sectional models, the time index (*t*) was added to consider the time of data collection (baseline, after 12 months or after 24 months) next to the patient index (*i*), explaining dependent variables for patient *i* given time *t [136, 137]*. Data analyses included patients with complete baseline data. Missing follow-up values were imputed using multiple imputations by chained equations separately by randomization treatment allocation (intervention and control group).

Lvm (independent variable) was operationalized as a dichotomous (receiving Lvm vs. not receiving Lvm within 24 months) and as a time referencing variable (never, once and over periods of one/or two years). The dependent variables were $HRQoL_{it}$ (SF-12-MCS, SF-12-PCS), $hospitalization_{it}$ (dichotomous: yes/no) and the delta (Δ = cost difference between baseline and 24 months after baseline) of *direct medical care costs*$_i$ and the following cost categories: *costs for physician treatments*$_i$ (GP and specialists), $hospitalization_i$, $medications_i$, *medical aids*$_i$, and $therapies_i$ (e.g., occupational, physical and speech therapy).

All models were adjusted for sociodemographic (age_{it}, sex_{it}, $living\ situation_{it}$) and clinical factors ($functional\ impairment_{it}$ (B-ADL), $dementia\ diagnosis_{it}$ (ICD-10: F00, F01, F02, F03, G30), $depression_{it}$ (GDS), $comorbidities_{it}$ (yes/no) according to the CCI, $multimorbidity_{it}$ (number of ICD-10 diagnoses), and $polypharmacy_{it}$ (i.e., $\geq$ 5 medications, yes/no) as well as the number of $potential\ drug\ interactions_{it}$ according to the Risk-Check tool CAVE of the ABDA-Database) to consider the context in which Lvm were prescribed and to minimize confounding [127]. A *lagged* Lvm_{it-1} variable was added, considering whether Lvm had also been present in the previous period [127]. For cost analyses, $baseline\ outcome\ values_{i,baseline}$ were included as a covariate to reduce residual and interindividual variances [127].

After using the Hausman test, random effects were used to adjust for individuals regarding the panel-specific structure for HRQoL and hospitalizations and GP practices concerning the delta of health care costs. Due to the highly skewed

distribution of cost data, standard errors and confidence intervals were determined using nonparametric bootstrapping (2,000 replications) [127, 135]. The models for panel-specific regression models are demonstrated in formulas (4), (5) and (6).

(4) $$HRQoL_{it} = \beta_0 + \beta_1 * Lvm_{it} + \beta_2 * age_{it} + \beta_3 * sex_{it} + \beta_4 * living\ situation_{it} + \beta_5 * dementia\ diagnoses_{it} + \beta_6 * BADL_{it} + \beta_7 * GDS_{it} + \beta_8 * comorbidities_{it} + \beta_9 * multimorbidity_{it} + \beta_{10} * polypharmacy_{it} + \beta_{11} * potential\ drug\ interactions_{it} + \beta_{12} * lagged\ Lvm_{it-1} + \beta_{13} * \text{DelpHi MV group assignement}_{it} + \in_{it}$$

(5) $$P(Hospitalization)_{it} = \frac{1}{1+e^{-(z_{it})}}$$, whereas

(5.1) $$z_{it} = \beta_0 + \beta_1 Lvm_{it} + \beta_2 age_{it} + \beta_3 sex_{it} + \beta_4 living\ situation_{it} + \beta_5 dementia\ diagnoses_{it} + \beta_6 BADL_{it} + \beta_7 GDS_{it} + \beta_8 comorbidities_{it} + \beta_9 multimorbidity_{it} + \beta_{10} polypharmacy_{it} + \beta_{11} potential\ drug\ interactions_{it} + \beta_{12} lagged\ Lvm_{it-1} + \beta_{13} \text{DelpHi MV group assignement}_{it} + \in_{it}$$

(6) $$\Delta\, Medical\ care\ costs_i = \beta_0 + \beta_1 * Lvm_i + \beta_2 * age_{ibaseline} + \beta_3 * sex_{ibaseline} + \beta_4 * living\ situation_{ibaseline} + \beta_5 * dementia\ diagnoses_{ibaseline} + \beta_6 * BADL_{ibaseline} + \beta_7 * GDS_{ibaseline} + \beta_8 * comorbidities_{ibaseline} + \beta_9 * multimorbidity_{ibaseline} + \beta_{10} * polypharmacy_{ibaseline} + \beta_{11} * potential\ drug\ interactions_{ibaseline} + \beta_{12} * lagged\ Lvm_{it-1} + \beta_{12} * medical\ care\ costs_{ibaseline} + \beta_{13} * \text{DelpHi MV group assignement}_i + \in_i$$

Sensitivity analyses were performed using multiple regression models for the most frequent Lvm cluster of drugs, i.e. *low-value antiphlogistics* and *analgesics*, *antidementia drugs*, *sedatives and hypnotics*, *antidepressants*, and *antipsychotics* [127]. The cluster of Lvm was implemented as independent variables (received vs not received within 24 months), and all models were adjusted as described above. All statistical analyses were conducted with STATA/IC software, version 16 [138].

4. Results

In the following section, first the cross-sectional and then the longitudinal results are presented. In each case, the sociodemographic and clinical characteristics of the samples are compared according to Lvm intake. The respective outcome variables are then described, deriving initial findings and trends. Finally, the associations and effects of Lvm intake are highlighted.

4.1. Results of the cross-sectional analyses

4.1.1. Sociodemographic and clinical sample characteristics

The study sample was primarily female (60%), on average 80 (SD 5.5) years old, mildly cognitively (MMSE mean score 22.2, SD 5.4), and functionally impaired (B-ADL mean score 3.7, SD 2.6). Study participants who received Lvm ($n = 159$) were, on average, marginal younger (79 vs 80 y, $p = 0.073$), were less cognitively impaired according to the MMSE (23.0 vs 21.7, $p = 0.013$), took more medications (9 vs 7, $p < 0.001$), and were more depressed (3.5 vs 3.0, $p = 0.032$), according to the GDS, compared to PwD who received no Lvm ($n = 357$). There were no significant differences for any of the other variables. Table 4 the cross-sectional sample characteristics.

4.1.2. Health-related quality of life, hospitalizations and health care costs

4.1.2.1. Health-related quality of life

Regarding the sample of the cross-sectional analyses, PwD receiving Lvm had lower HRQoL regarding the QoL-AD (2.66 vs. 2.77, p=0.234) and the SF-12 for both the mental (52.4 vs. 53.1, p=0.490) and the physical (39.8 vs. 42.7, p=0.007) dimension than PwD not receiving Lvm, demonstrating statistical significance for the physical health state in particular. Table 5 and Figure 9 summarize the average HRQoL among PwD who received and PwD who did not receive Lvm.

Table 4: Sociodemographic and clinical characteristics of the total sample and subsample

	Total sample	**PwD receiving Lvm**		***p value***
		Yes	**No**	
	n=516	**n=159**	**n=357**	
Age				
Mean (SD)	80.0 (5.5)	79.3 (5.5)	80.3 (5.5)	0.073‡
95%CI	(79.5 – 80.5)	(78.5 – 80.2)	(79.7 – 80.9)	
Sex n (%)				
Female	307 (59.5)	104 (65.4)	203 (56.9)	0.080§
95%CI	(55.3 – 63.7)	(58.0 – 72.8)	(51.7 – 62.0)	
MMSE				
Mean (SD)	22.2 (5.4)	23.0 (4.4)	21.7 (5.7)	**0.013**‡
95%CI	(21.7 – 22.7)	(22.3 – 23.7)	(21.1 – 22.4)	
Living situation n (%)				
Alone	260 (50.9)	84 (52.8)	176 (50.0)	0.568§
95%CI	(46.5 – 55.2)	(45.1 – 60.6)	(44.8 – 55.2)	
Number of ICD-10 diagnoses				
Mean (SD)	13.2 (7.8)	13.7 (7.3)	12.9 (8.0)	0.318‡
95%CI	(12.5 – 13.8)	(12.5 – 14.8)	(12.1 – 13.8)	
Number of drugs taken				
Mean (SD)	7.3 (3.6)	8.8 (4.1)	6.7 (3.1)	**< 0.001**‡
95%CI	(7.0 – 7.78)	(8.2 – 9.4)	(6.3 – 7.0)	
Charlson Score				
Mean (SD)	3.3 (2.3)	3.3 (2.1)	3.4 (2.3)	0.632‡
95%CI	(3.1 – 3.5)	(2.9 – 3.6)	(3.1 – 3.6)	
B-ADL*				
Mean (SD)	3.7 (2.6)	3.5 (2.3)	3.7 (2.7)	0.357‡
95%CI	(3.5 – 3.9)	(3.2 – 3.9)	(3.5 – 4.1)	
GDS*				
Mean (SD)	3.2 (2.5)	3.5 (2.8)	3.0 (2.3)	**0.032**‡
95%CI	(3.0 – 3.4)	(3.1 – 4.0)	(2.8 – 3.3)	

Abbreviations: *Lvm* Low-value medications; *MMSE* Mini-Mental State Examination, range 0-30, higher score indicates better cognitive function; *B-ADL* Bayer-Activities of Daily Living Scale, range 0-10, lower score indicates better performance; *GDS* Geriatric Depression Scale, sum score 0-15, score ≥6 indicates depression; *ICD* International Statistical Classification of Diseases and Related Health Problems; *SD* standard deviation; *PwD* Persons with Dementia
Missing data can occur
‡Differences in means were evaluated by using t-test
§Differences in proportions were evaluated by using Fisher exact test
Values in bold indicate $p < 0.05$

Source: Own Table.

Table 5: Average health-related quality of life among persons living with dementia who received and did not receive low-value medications

	Total sample	PwD receiving Lvm		*p value**‡
		Yes	No	
QoL-AD	**n=510**	**n=159**	**n=351**	
Mean (SD)	2.70 (0.58)	2.66 (0.57)	2.72 (0.58)	0.234
95%CI	(2.65 – 2.75)	(2.57 – 2.75)	(2.66 – 2.78)	
Mental HRQoL (SF-12-MCS)	**n=457**	**n=142**	**n=315**	
Mean (SD)	52.92 (9.88)	52.44 (11.26)	53.13 (9.20)	0.490
95%CI	(52.01 – 53.83)	(50.58 – 54.31)	(52.11 – 54.15)	
Physical HRQoL (SF-12-PCS)	**n=457**	**n=142**	**n=315**	
Mean (SD)	41.81 (10.51)	39.85 (10.17)	42.70 (10.55)	**0.007**
95%CI	(40.85 – 42.78)	(38.16 – 41.53)	(41.53 – 43.87)	

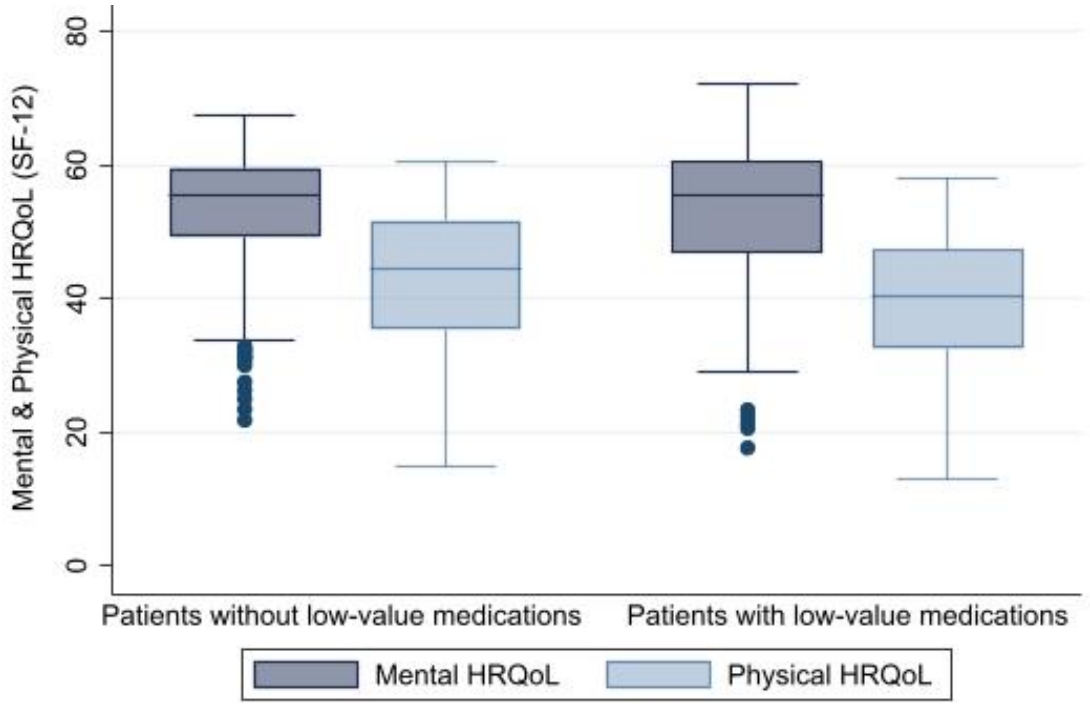
Abbreviations: *Lvm* Low-value medications; *PwD* Persons with Dementia; *HRQoL* Health-Related Quality of Life; *QoL-AD* Quality of Life in Alzheimer's Diseases, mean sum score 1–4, higher score indicates better quality of life; *SF-12* Short Form Health Survey mental/physical dimension, range 0-100, higher score indicates better quality of life; *SD* standard deviation; *CI* confidence interval

*****Referring to PwD who received no Lvm vs at least one Lvm

‡Differences in means were evaluated by using t-test

Values in bold indicate $p < 0.05$

Source: Own Table.



Abbreviations: Lvm, Low-value medications; HRQoL, health-related quality of life; PwD Persons with Dementia; SF-12 Short Form Health Survey mental/physical dimension, range 0-100, higher score indicates better quality of life

Figure 9: Differences in mental and physical health-related quality of life by Lvm.

Source: Own figure.

4.1.2.2. Resource utilization and health care costs

PwD who received at least one Lvm had higher resource use of medical treatments. Significant differences were observed in specialist consultations regarding the prevalence (32 vs 23%, $p = 0.045$) and frequency (1.2 vs 0.6, $p = 0.037$). Moreover, participants with Lvm had more inpatient treatments (39 vs 26%, $p = 0.007$), especially acute (28 vs 19%, $p = 0.019$) and planned (14 vs 7%, $p = 0.019$) in-hospital treatments, and stayed on average more days in hospitals (6 vs 3 days, $p = 0.009$) than patients without Lvm intake. They also received, on average, significantly more anti-dementia drugs (37 vs 26%, $p = 0.020$) and used other outpatient treatments more often (68 vs 59%, $p = 0.039$). All results on the percentage and frequency of health care resource utilization are depicted in Table 6. Figure 10 compares PwD with and without Lvm regarding in-patient treatments and days spent in the hospital.

The total cost for used medications was 181,153 € for the total sample, of which Lvm accounts for 29,983 € (17%) and the remaining medications for 151,170 € (83%). Payers' expenditures for patients receiving Lvm were statistically significantly higher than for patients who did not receive Lvm (8,514 € vs 5,539 €, $p < 0.001$). This trend was also evident for specialists' spending (382 € vs 305 €, $p = 0.035$), spending for inpatient treatments (4,501 € vs 2,380 €, $p = 0.003$), especially in spending for acute in-hospital treatments (2,996 € vs 1,749 €, $p = 0.031$), and medication costs (2,450 € vs 1,538 €, $p < 0.001$). Cost differences between Lvm recipients and Lvm non-recipients are presented in Table 7. Figure 11 visualizes the direct costs for payers broken down by medical treatments for PwD with and without Lvm.

Table 6: Percentage and amount of medical treatment utilization by persons living with dementia who received and did not receive low-value medications

Health resource use	Total sample	PwD receiving Lvm		*p value**
		Yes	No	
	n = 516	n = 159	n = 357	
Medical Treatments				
Percentage of utilization, n (%)				
Outpatient physician treatment	516 (100.0)	159 (100.0)	357 (100.0)	
GP	516 (100.0)	159 (100.0)	357 (100.0)	
Specialists	128 (25.5)	48 (31.6)	80 (22.8)	**0.045**§
95%CI	(21.6 – 29.3)	(24.2 – 39.0)	(18.4 – 27.2)	
Inpatient treatment	153 (30.2)	61 (38.6)	92 (26.4)	**0.007**§
95%CI	(26.2 – 34.2)	(31.0 – 46.2)	(21.8 – 31.1)	
In-hospital treatment	142 (28.3)	58 (37.42)	84 (24.21)	**0.004**
95%CI	(24.3 – 32.2)	(29.8 – 45.1)	(19.7 – 28.7)	
Acute in-hospital treatment	109 (21.8)	44 (28.4)	65 (18.8)	**0.019**§
95%CI	(18.2 – 25.4)	(21.3 – 35.5)	(14.7 – 23.0)	
Planned in-hospital treatment	47 (9.4)	22 (14.3)	25 (7.2)	**0.019**§
95%CI	(6.8 – 11.9)	(08.7 – 19.8)	(4.5 – 9.9)	
Rehabilitation	31 (6.1)	12 (7.6)	19 (5.5)	0.424§
95%CI	(4.0 – 8.2)	(03.5 – 11.7)	(3.1 – 07.9)	
Medications	484 (98.4)	158 (99.4)	326 (97.9)	0.447§
95%CI	(97.3 – 99.5)	(98.1 – 100)	(96.4 – 99.4)	
Anti-dementia drugs	144 (29.5)	58 (36.5)	86 (26.1)	**0.020**§
95%CI	(25.5 – 33.6)	(29.0 – 44.0)	(21.4 – 30.9)	
Medical Aids	499 (98.6)	151 (97.4)	348 (99.2)	0.209§
95%CI	(97.6 – 99.6)	(94.9 – 99.9)	(98.2 – 100)	
Other outpatient therapies	315 (61.6)	108 (68.4)	207 (58.6)	**0.039**§
95%CI	(57.4 – 65.9)	(61.1 – 75.6)	(53.5 – 63.8)	
Frequency of utilization, mean (SD)				
Number of GP contacts	7.00 (6.4)	6.9 (5.3)	7.1 (6.8)	0.745‡
95%CI	(6.4 – 7.5)	(6.0 – 7.7)	(6.3 – 7.8)	
Number of specialists contacts	0.8 (2.9)	1.2 (4.5)	0.6 (1.6)	**0.037**‡
95%CI	(0.6 – 1.1)	(0.5 – 2.0)	(0.5 – 0.8)	
Days stayed in-hospital per year	4.0 (9.6)	5.7 (11.2)	3.3 (8.6)	**0.009**‡
95%CI	(3.2 – 4.8)	(3.9 – 7.4)	(2.3 – 4. 2)	
Number of medical aids	4.7 (2.7)	5.0 (2.8)	4.6 (2.7)	0.138‡
95%CI	(4.5 – 5.0)	(4.6 – 5.4)	(4.3 – 4.9)	
Number of outpatient therapy visits	11.2 (35.7)	10.8 (17.0)	11.3 (41.4)	0.881‡
95%CI	(8.1 – 14.3)	(8.2 – 13.5)	(7.0 – 15.7)	

Abbreviations: *CI* confidence interval; *GP* General practitioner; *Lvm* Low-value medications; *SD* standard deviation; *PwD* Persons with Dementia
Missing data can occur
‡Differences in means were evaluated by using t-test
§Differences in proportions were evaluated by using Fisher exact test
Values in bold indicate $p < 0.05$

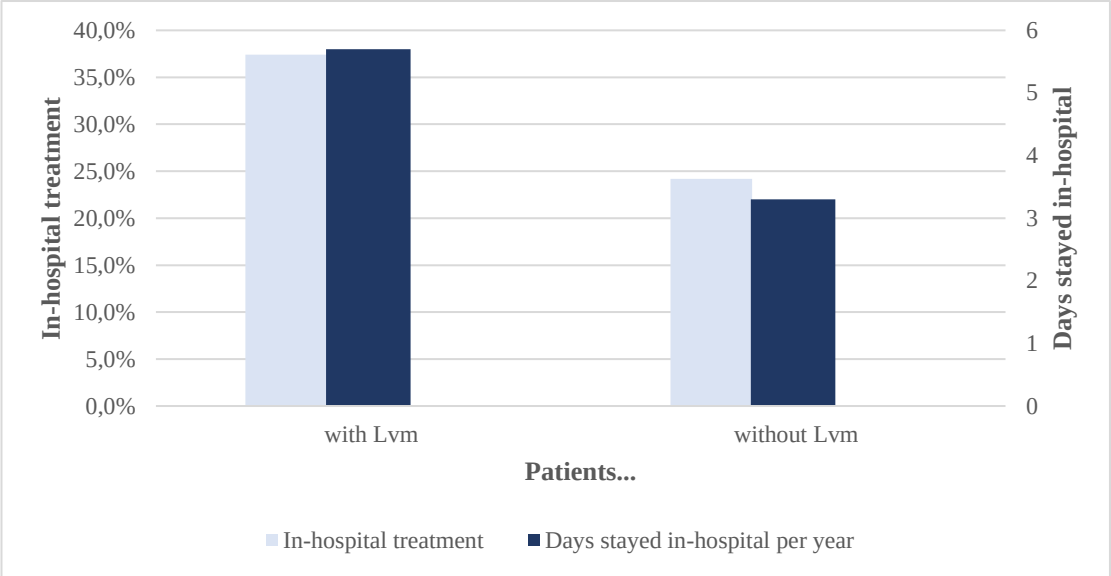
Source: Own Table.

Table 7: Direct costs of medical treatments for persons living with dementia who received and did not receive low-value medications

Health care costs [€]	Total sample	PwD receiving Lvm		*p value**‡
		Yes	No	
	n = 516	n = 159	n = 357	
Medical Treatments	6,501 (7,899)	8,514 (9,260)	5,539 (6,973)	**< 0.001**
95%CI	(5,778 – 7,224)	(7,015 – 10,013)	(4,762 – 6,316)	
Outpatient physician treatment	499 (424)	549 (472)	477 (400)	0.074
95%CI	(462 – 537)	(475 – 623)	(435 – 518)	
GP	170 (155)	167 (128)	171 (165)	0.745
95%CI	(157 – 183)	(147 – 187)	(154 – 189)	
Specialists	329 (384)	382 (451)	305 (347)	**0.035**
95%CI	(296 – 362)	(312 – 453)	(269 – 341)	
Inpatient treatment	2,994 (6,883)	4,501 (8,349)	2,380 (6,018)	**0.003**
95%CI	(2,386 – 3,603)	(3,022 – 5,680)	(1,738 – 3,022)	
In-hospital treatment	2,896 (6,910)	4,097 (8,072)	2,357 (6,258)	**0.009**
95%CI	(2,287 – 3,505)	(2,812 – 5,382)	(1,692 – 3,022)	
Acute treatment	2,136 (5,952)	2,996 (6,875)	1,749 (5,455)	**0.031**
95%CI	(1,611 – 2,660)	(1,901 – 4,090)	(1,170 – 2,329)	
Planned treatment	759 (3,492)	1,101 (4,049)	607 (3,209)	0.144
95%CI	(452 – 1,065)	(457 – 1,746)	(268 – 946)	
Rehabilitation	175 (769)	254 (918)	140 (690)	0.128
95%CI	(108 – 243)	(108 – 400)	(67 – 213)	
Medications	1,833 (1,919)	2,450 (2,372)	1,538 (1,581)	**< 0.001**
95%CI	(1,663 – 2,003)	(2,079 – 2,822)	(1,368 – 1,709)	
Medical Aids	933 (1,071)	933 (984)	932 (1,108)	0.992
95%CI	(839 – 1,026)	(777 – 1,090)	(816 – 1,049)	
Other outpatient treatment	130 (772)	120 (509)	134 (864)	0.844
95%CI	(63 – 197)	(39 – 200)	(44 – 224)	

Abbreviations: *CI* confidence interval; *GP* General practitioner; *Lvm* Low-value medications; *SD* standard deviation; *PwD* Persons with Dementia
Missing data can occur
*****Referring to PwD who received no Lvm vs at least one Lvm
‡Differences in means were evaluated by using t-test
Values in bold indicate $p < 0.05$

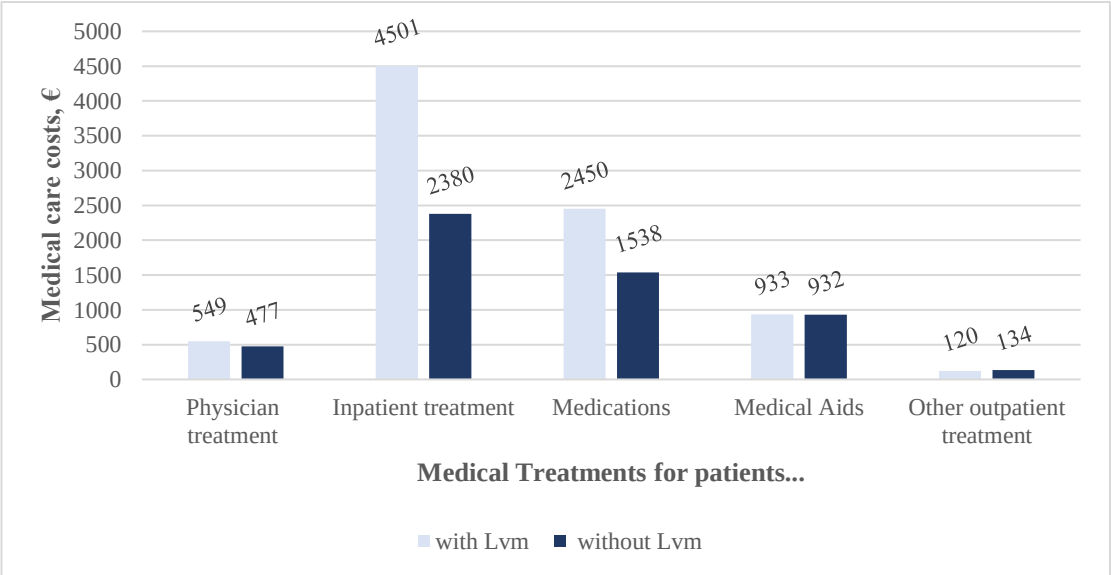
Source: Own Table.



Abbreviations: Lvm, Low-value medications

Figure 10: In-hospital treatments for Patientes with & without low-value medications.

Source: Own figure.



Abbreviations: Lvm, Low-value medications

Figure 11: Medical care costs for patientes with & without low-value medications.

Source: Own figure.

4.1.3. Associations between low-value medications and PRO

The multivariable regression analyses revealed that PwD who received Lvm treatments had a significantly lower HRQoL, represented by a lower QoL-AD score (B=–0.07; 95% CI –0.14–0.01). Concerning hospitalization, receiving at least one Lvm treatment was associated with significantly higher odds of hospitalization within the past 12 months (OR=2.06; 95% CI 1.26–3.39).

Patients who received Lvm had significantly higher medical treatment costs (b = 2959 €; 95% CI 1136–4783; p = 0.001) due to significantly higher costs for inpatient treatments (b = 1911 €; 95% CI 376–3443; p = 0.015) and medications (b = 905 €; 95% CI 454–1357; p < 0.001). In contrast, there were no significant findings between PwD receiving Lvm and costs for outpatient physician treatments, medical aids, and other outpatient treatments. The latter model was no longer significant. Table 8 summarizes the results of the multiple regression analyses.

Table 8: Associations between Lvm and health-related quality of life, hospitalizations and direct medical care costs.

	PwD receiving Lvm Yes		
Outcome variable	**b**	**95% CI**	***p value***
Health-related quality of life			
QoL-AD, (N=450)	-0.07	-0.14 – -0.01	**0.024**
Mental HRQoL (SF-12-MCS) , (N=417)	0.12	-1.73 – 1.98	0.896
Physical HRQoL (SF-12-PCS), (N=417)	-1.58	-3.45 – 0.29	0.098
Hospitalization			
In-hospital treatment, (N=444)	2.06‡	1.26‡ – 3.39‡	**0.004**
Health care costs from payers' perspective†			
Medical care costs†, (N=427)	2,923	1,452 – 4,394	< **0.001**
Physicians†, (N= 450)	64	-17 – 145	0.122
In-hospital, (N=437)	1,828	492 – 3,165	**0.007**
Medications†, (N=449)	908	541 – 1,277	< **0.001**
Medical aids†, (N= 444)	-14	-229 – 200	0.895
Therapies†, (N=450)	30	-57 – 118	0.498

Abbreviations: *Lvm* Low-value medications; *PwD* Persons with Dementia; *HRQoL* Health-Related Quality of Life; *QoL-AD* Quality of Life in Alzheimer's Diseases, mean sum score 1–4, higher score indicates better quality of life; *SF-12* Short Form Health Survey mental/physical dimension, range 0-100, higher score indicates better quality of life; b observed coefficient; *CI* confidence interval

*Regression models; standard errors were estimated with a nonparametric bootstrapping (2,000 replications) Models were adjusted for socio-demographic and clinical variables: age, sex, cognition (MMSE), functional impairment (B-ADL), depression (GDS), comorbidities (CCI) and number of ICD-10 diagnoses

‡Odds ratio (95% CI) p values less than 0.05 are highlighted in bold

4.2. Results of the longitudinal analyses

4.2.1. Sociodemographic and clinical sample characteristics at baseline

Table 9 summarizes the participants' baseline characteristics. PwD who received Lvm at baseline were slightly younger, more likely female, more depressed, and more affected by polypharmacy and potential drug interactions compared to PwD who received no Lvm treatments at baseline. There were no significant differences for any other variables.

4.2.2. Prevalence of low-value medications

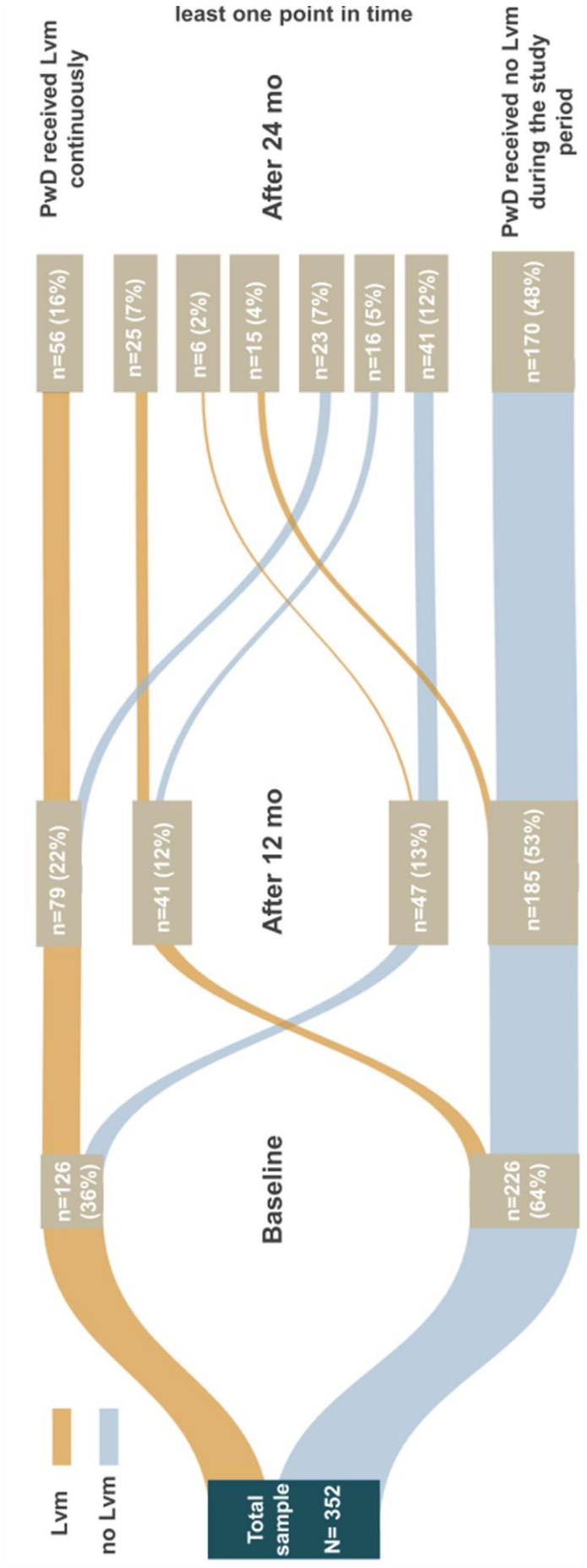
Over 24 months, more than every second PwD (n=182, 52%) received Lvm at least once. Sixteen percent of PwD (n=56) received Lvm continuously over 24 months, whereas 48% (n=170) did not receive any Lvm, indicating that another 126 (36%) received Lvm sporadically but not continuously over 24 months. More than 90% of those receiving Lvm at baseline were on nonrecommended antiphlogistics and analgesics (n=43, 34%), sedatives and hypnotics, such as benzodiazepines (n=22, 18%), low-value antidepressants (n=17, 14%), or nonguideline medications for dementia (n=32, 25%). Lvm prevalence decreased over time from 36% (n=126) at baseline to 34% (n=124) and 29% (n=102) after 12 and 24 months, respectively. Sensitivity analyses revealed no statistically significant differences between the intervention and control groups (Supplementary Tables 3 and 4). Figure 12 demonstrates the trajectories of Lvm intake over time.

Table 9: Sociodemographic and clinical characteristics of the total sample and subsample

	Total sample	**PwD receiving Lvm**		***p value****
		Yes	**No**	
	n = 352	**n = 126**	**n = 226**	
Age				
Mean (SD)	80.2 (5.3)	79.3 (5.0)	80.7 (5.4)	**0.022**‡
95%CI	(79.6 – 80.7)	(78.4 – 80.2)	(80.0 – 81.4)	
Sex n (%)				
Female	215 (61.1)	86 (68.3)	129 (57.1)	**0.041**§
95%CI	(56.0 – 66.2)	(60.1 – 76.4)	(50.6 – 63.6)	
MMSE				
Mean (SD)	22.4 (5.1)	22.8 (4.2)	22.2 (5.5)	0.234‡
95%CI	(21.9 – 22.9)	(22.1 – 23.6)	(21.4 – 22.9)	
Living situation n (%)				
Alone	178 (50.6)	69 (54.8)	109 (48.2)	0.267§
95%CI	(45.3 – 55.8)	(46.0 – 63.5)	(41.7 – 54.8)	
Number of ICD-10 diagnoses				
Mean (SD)	14.0 (7.8)	14.4 (7.7)	13.8 (7.9)	0.469‡
95%CI	(13.2 – 14.8)	(13.1 – 15.8)	(12.8 – 14.8)	
Number of drugs taken				
Mean (SD)	7.4 (3.5)	8.6 (3.9)	6.7 (3.1)	**<0.001**‡
95%CI	(7.0 – 7.7)	(7.9 – 9.3)	(6.3 – 7.1)	
Patients with polypharmacy†, n (%)				
Polypharmacy	290 (83.4)	115 (91.3)	175 (77.4)	**<0.001**§
95%CI	(78.4 – 86.4)	(86.3 – 96.2)	(72.0 – 82.9)	
Number of potential drug interactions				
Mean (SD)	0.6 (0.9)	0.8 (1.0)	0.5 (0.8)	**0.007**‡
95%CI	(0.5 – 0.7)	(0.6 – 1.0)	(0.4 – 0.6)	
Charlson Score				
Mean (SD)	3.4 (2.3)	3.3 (2.2)	3.4 (2.3)	0.675‡
95%CI	(3.1 – 3.6)	(2.9 – 3.7)	(3.1 – 3.7)	
B-ADL*				
Mean (SD)	3.5 (2.5)	3.4 (2.1)	3.6 (2.7)	0.419‡
95%CI	(3.3 – 3.8)	(3.0 – 3.8)	(3.3 – 4.0)	
GDS*				
Mean (SD)	3.1 (2.3)	3.5 (2.7)	2.8 (2.0)	**0.015**‡
95%CI	(2.8 – 3.3)	(3.0 – 3.9)	(2.6 – 3.1)	

Abbreviations: *Lvm* Low-value medications; *MMSE* Mini-Mental State Examination, range 0-30, higher score indicates better cognitive function; *B-ADL* Bayer-Activities of Daily Living Scale, range 0-10, lower score indicates better performance; *GDS* Geriatric Depression Scale, sum score 0-15, score ≥6 indicates depression; *ICD* International Statistical Classification of Diseases and Related Health Problems; *SD* standard deviation; *PwD* Persons with Dementia
*referring to PwD who received no Lvm vs. at least one Lvm † Defined as ≥ 5 prescribed medications ‡ Differences in means: T-Test two-tailed § Differences in proportions: Fisher's exact Tests p values less than 0.05 are highlighted in bold

Source: Own Table.



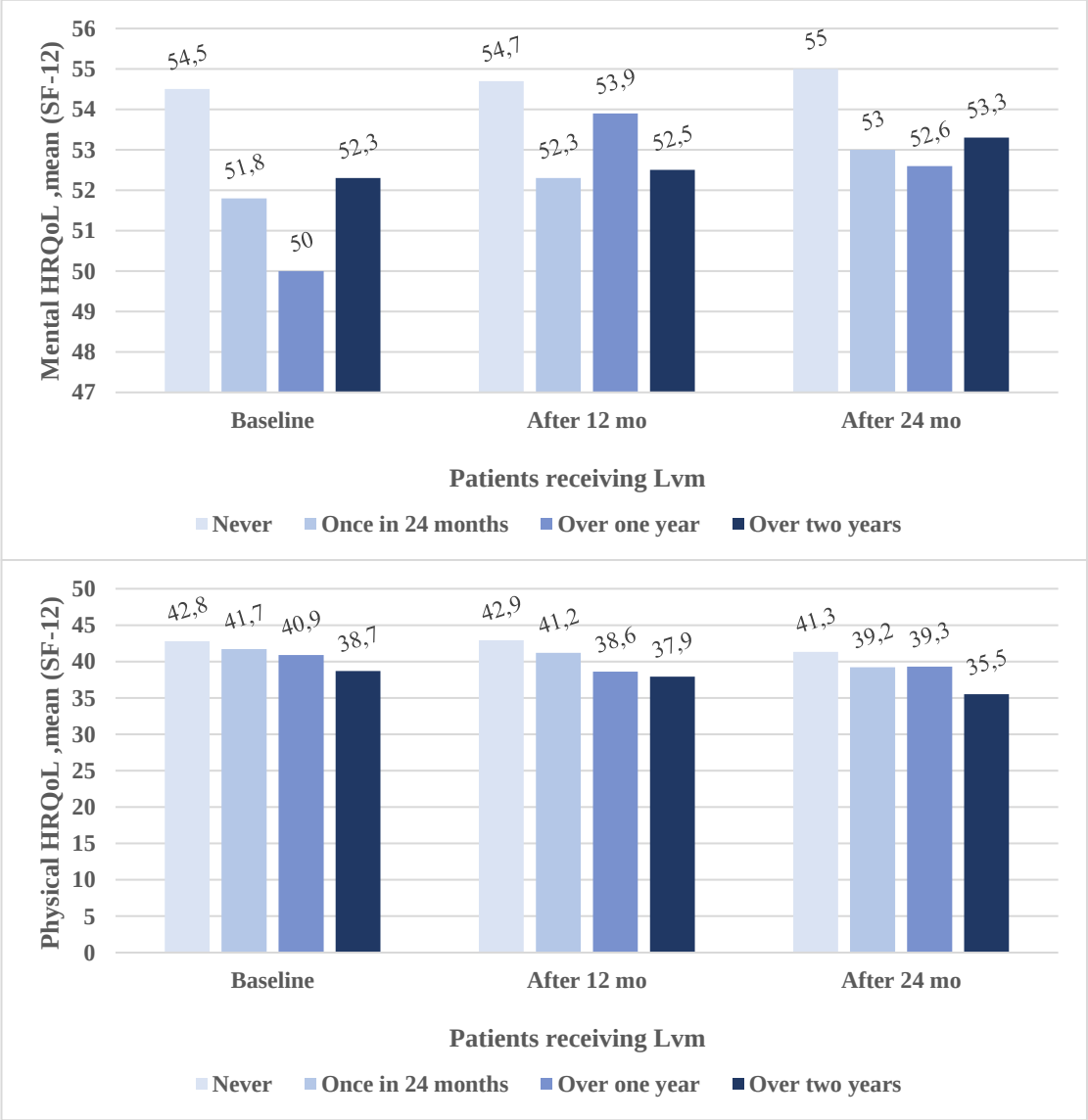
Abbreviations: Lvm, Low-value medications; PwD Persons with Dementia; mo months

Figure 12: Trajectories of Lvm over 24 months.

Source: Own figure.

4.2.3. Health-related quality of life, hospitalizations and health care costs

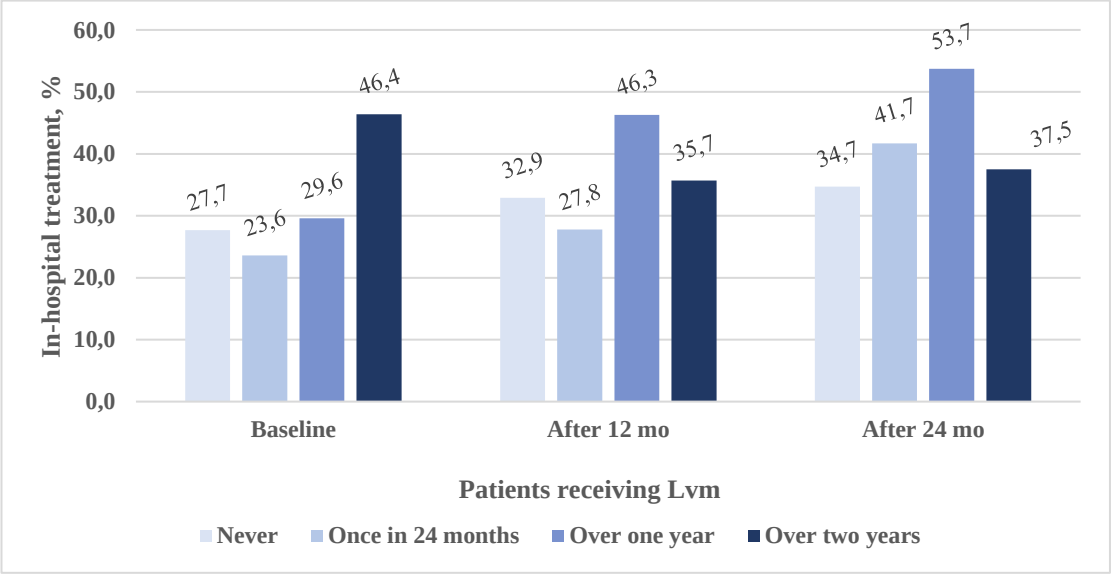
At baseline, PwD receiving Lvm had lower mental (50-52 vs. 55, p=0.011) and physical HRQoL (39-42 vs. 43, p=0.077), were more likely to be hospitalized (up to 45% vs. 28%, p=0.029) and incurred higher costs (up to €12,008 vs. €7,052, p=0.001) than those not receiving Lvm. Decreasing physical HRQoL 24 months after baseline was more pronounced in PwD receiving Lvm than in PwD not receiving Lvm (-6.1 vs. -3.5%), with the greatest decrease in PwD taking Lvm continuously over 24 months (-8.3%). Figure 13 illustrates HRQoL-dimension by Lvm-intake at different time points.



Abbreviations: Lvm, Low-value medications; SF-12 Short Form Health Survey mental/physical dimension, range 0-100, higher score indicates better quality of life;
Figure 13: Health-related quality of live by patients' Lvm-intake over 24 months.

Source: Own figure.

Hospitalizations increased more intensively in patients who took Lvm at least once (from 24 to 42%; +77%) or over one year (from 30 to 54%) than in PwD not taking Lvm (from 28 to 35%; +26%). PwD continuously taking Lvm already had a very high hospitalization rate at baseline (46%), which slightly decreased to 38% (-19%) 24 months after baseline; this decrease was also reflected in the health care costs, which is summarized in Figures 14 and 15.

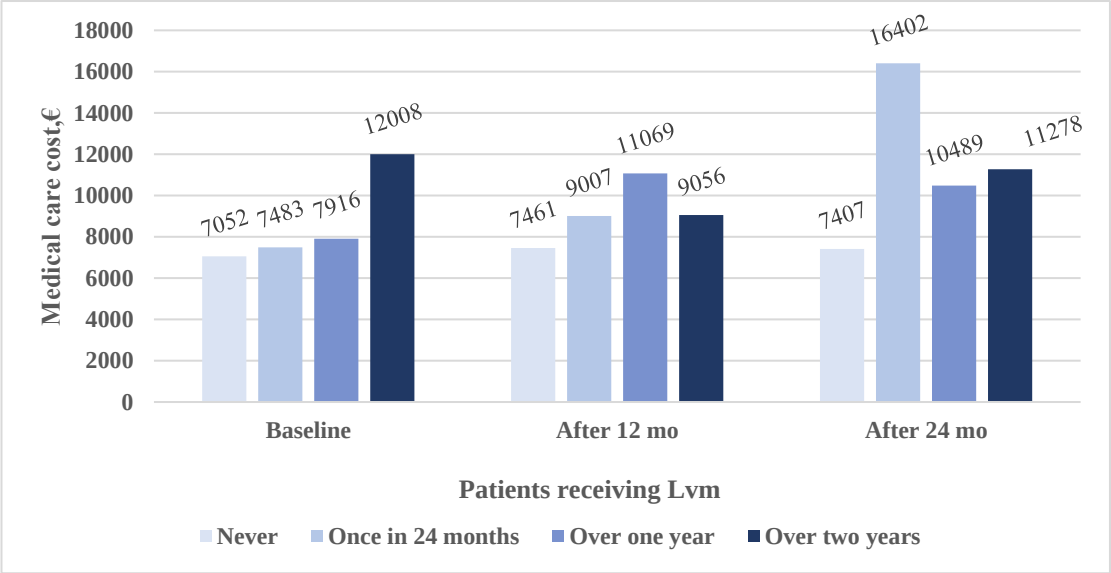


Abbreviations: Lvm, Low-value medications

Figure 14: Hospitalizations by patients' Lvm-intake over 24 months.

Source: Own figure.

PwD receiving Lvm briefly had a greater increase in health care costs over time (Lvm once: +€8,919; Lvm over one year (+€2,573) compared with those not receiving Lvm (+€355). PwD continuously taking Lvm over 24 months already had twice as high costs at baseline compared to those without Lvm (€12,008 vs. €7,052, p≤0.001), which slightly decreased over time (-730€). Group differences over time are summarized in Tables 10 and 11.



Abbreviations: Lvm, Low-value medications
Figure 15: Medical care costs by patients' Lvm-intake over 24 months.

Source: Own figure.

Table 10: Group differences in health resource use at baseline, 12 months, and 24 months for PwD with & without Lvm

Health resource use at baseline	**PwD receiving Lvm**		***p value****
	Yes n = 126	**No n = 226**	
Medical Treatments			
Frequency of utilization, mean (SD)			
GP	7.0 (5.4)	6.9 (6.3)	0.927
95%CI	(6.1 – 8.0)	(6.1 – 7.8)	
Specialists	1.3 (4.8)	0.7 (1.7)	0.107
95%CI	(0.4 – 2.1)	(0.5 – 0.9)	
Other specialists	6.5 (5.1)	5. 7 (6.1)	0.182
95%CI	(5.6 – 7.4)	(4.9 – 6.5)	
In-hospital treatment	5.5 (9.7)	3.1 (8.1)	**0.017**
95%CI	(3.7 – 7.2)	(2.1 – 4.2)	
Medications	8.6 (3.9)	6.7 (3.1)	**<0.001**
95%CI	(7.9 – 9.3)	(6.3 – 7.1)	
Medical Aids	4.8 (2.7)	4.5 (2.6)	0.371
95%CI	(4.3 – 5.3)	(4.2 – 4.9)	
Other outpatient therapies	3.1 (7.5)	4.5 (13.5)	0.288
95%CI	(1.8 – 4.4)	(2.7 – 6.3)	

Continued Table 10: Outcome-related group differences at baseline, 12 months, and 24 months among PwD who never received Lvm, received Lvm once in 24 months, received Lvm for 1 year, or received Lvm for 2 years

Health resource use after 12 mo	**PwD receiving Lvm**		
	Yes	**No**	***p value***‡*
	n = 126	**n = 226**	
Medical Treatments			
Frequency of utilization, mean (SD)			
GP	6.5 (4.7)	5.5 (4.0)	**0.046**
95%CI	(5.6 – 7.3)	(5.0 – 6.0)	
Specialists	1.3 (2.1)	0.9 (2.1)	0.157
95%CI	(0.9 – 1.6)	(0.7 – 1.2)	
Other specialists	5.5 (5.8)	4.9 (4.9)	0.305
95%CI	(4.4 – 6.5)	(4.2 – 5.5)	
In-hospital treatment	4.6 (17.4)	4.0 (12.4)	0.715
95%CI	(1.4 – 7.7)	(2.4 – 5.6)	
Medications	9.4 (4.1)	6.8 (3.3)	**<0.001**
95%CI	(8.6 – 10.1)	(6.4 – 7.2)	
Medical Aids	6.0 (3.0)	5.4 (3.0)	0.112
95%CI	(5.4 – 6.5)	(5.0 – 5.8)	
Other outpatient therapies	7.4 (3.2)	6.5 (3.1)	**0.017**
95%CI	(6.7 – 8.0)	(6.1 – 6.9)	
Health resource use after 24 mo	**PwD receiving Lvm**		
	Yes	**No**	***p value****
	n = 126	**n = 226**	
Medical Treatments			
Frequency of utilization, mean (SD)			
GP	5.6 (6.3)	5.8 (8.7)	0.849
95%CI	(4.4 – 6.9)	(4.7 – 6.9)	
Specialists	0.7 (1.3)	0.6 (1.2)	0.709
95%CI	(0.4 – 0.9)	(0.5 – 0.8)	
Other specialists	4.9 (6.0)	4.6 (5.0)	0.618
95%CI	(3.7 – 6.1)	(4.0 – 5.2)	
In-hospital treatment	7.1 (15.1)	5.4 (23.2)	0.515
95%CI	(4.1 – 10.0)	(2.5 – 8.3)	
Medications	9.6 (4.0)	6.9 (3.1)	**<0.001**
95%CI	(6.5 – 7.3)	(8.8 – 10.3)	
Medical Aids	7.4 (3.2)	6.5 (3.1)	**0.017**
95%CI	(6.7 – 8.0)	(6.1 – 6.9)	
Other outpatient therapies	8.4 (24.6)	6.6 (17.7)	0.451
95%CI	(3.5 – 13.2)	(4.4 – 8. 8)	

Abbreviations: *CI* confidence interval; *GP* General practitioner; *Lvm* Low-value medications; *SD* standard deviation; *PwD* Persons with Dementia

*****Referring to PwD who received no Lvm vs at least one Lvm

‡Differences in means were evaluated by using t-test

Values in bold indicate $p < 0.05$

Table 11: Outcome-related group differences at baseline, 12 months, and 24 months among PwD who never received Lvm, received Lvm once in 24 months, received Lvm for 1 year, or received Lvm for 2 years

Outcome-related group differences at baseline	**PwD receiving Lvm**				
	Never, n=170 (48%)	**Once in 24 months, n=72 (20%)**	**Over one year, n=54 (15%)**	**Over two years, n=56 (16%)**	***p value***
Mental HRQoL (SF-12-MCS), mean (SD)	54.5 (7.7)	51.8 (10.3)	50.0 (9.8)	52.3 (10.6)	**0.011**†
95%CI	(53.2 – 55.6)	(49.4 – 54.2)	(47.4 – 52.6)	(49.6 – 55.1)	
Physical HRQoL (SF-12-PCS), mean (SD)	42.8 (10.5	41.7 (10.1)	40.9 (9.7)	38.7 (9.7)	0.077†§
95%CI	(41.2 – 44.4)	(39.3 – 44.0)	(38.4 – 43.5)	(36.2 – 41.3)	
Hospitalization (yes), n (%)	47 (27.7)	17 (23.6)	16 (29.6)	26 (46.4)	**0.029***
95%CI	(20.9 – 34.4)	(13.8 – 33.5)	(17.4 – 41.9)	(33.3 – 59.5)	
Health care costs (€), mean (SD)	7,052 (7,458)	7,483 (7,848)	7916 (6,825)	12,008 (10,744)	**0.001**†
95%CI	(5,927 – 8,177)	(5,664 – 9,302)	(6,089 – 9,742)	(9,185 – 14,832)	
Outcome-related group differences after 12 mo	**PwD receiving Lvm**				
	Never, n=170 (48%)	**Once in 24 months, n=72 (20%)**	**Over one year, n=54 (15%)**	**Over two years, n=56 (16%)**	***p value***
Mental HRQoL (SF-12-MCS), mean (SD)	54.7 (7.4)	52.3 (10.3)	53.9 (7.3)	52.5 (9.0)	
95%CI	(53.6 – 55.8)	(49.9 – 54.7)	(51.9 – 55.8)	(50.1 – 54.9)	0.140†
Δ‡ in %	+0.4	+1.0	+7.8	+0.4	
Physical HRQoL (SF-12-PCS), mean (SD)	42.9 (9.6)	41.2 (8.7)	38.6 (10.8)	37.9 (11.9)	
95%CI	(41.4 – 44.3)	(39.2 – 43.2)	(35.7 – 41.5)	(34.8 – 41.1)	**0.003**†
Δ‡ in %	+0.2	-1.2	-5.6	-2.1	
Hospitalization (yes), n (%)	56 (32.9)	20 (27.8)	25 (46.3)	20 (35.7)	
95%CI	(25.9 – 40.0)	(17.4 – 38.2)	(33.0 – 59.6)	(23.1 – 48.3)	0.174*
Δ‡ in %	+19.1	+17.6	+56.3	-23.1	
Health care costs (€), mean (SD)	7,461 (7,862)	9,007 (16,538)	11,069 (21,695)	9,056 (7,167)	
95%CI	(6,275 – 8,647)	(5,175 – 12,841)	(5,263 – 16,876)	(7,173 – 10,940)	0.328†
Δ‡ in €	+409	+1,524	+3,153	-2,952	

Continued Table 11: Outcome-related group differences at baseline, 12 months, and 24 months among PwD who never received Lvm, received Lvm once in 24 months, received Lvm for 1 year, or received Lvm for 2 years

Outcome-related group differences after 24 mo	PwD receiving Lvm				*p value*
	Never, n=170 (48%)	**Once in 24 months, n=72 (20%)**	**Over one year, n=54 (15%)**	**Over two years, n=56 (16%)**	
Mental HRQoL (SF-12-MCS), mean (SD)	55.0 (7.7)	53.0 (9.3)	52.6 (9.4)	53.3 (9.7)	
95%CI	(53.8 – 56.1)	(50.8 – 55.1)	(50.1 – 55.1)	(50.7 – 55.8)	0.177†
Δ¶ in %	+0.9	+2.3	+5.2	+1.9	
Physical HRQoL (SF-12-PCS), mean (SD)	41.3 (9.9)	39.2 (10.2)	39.3 (9.0)	35.5 (10.6)	
95%CI	(39.8 – 42.8)	(36.9 – 41.6)	(36.9 – 41.7)	(32.7 – 38.3)	**0.002**†
Δ¶ in %	-3.5	-6.0	-3.9	-8.3	
Hospitalization (yes), n (%)	59 (34.7)	30 (41.7)	29 (53.7)	21 (37.5)	
95%CI	(27.5 – 41.9)	(30.2 – 53.1)	(40.4 – 67.0)	(24.8 – 50.2)	0.093*§
Δ¶ in %	+25.5	+76.5	+81.3	-19. 2	
Health care costs (€), mean (SD)	7,407 (6,807)	16,402 (36,725)	10,489 (12,545)	11,278 (13,014)	
95%CI	(6,380 – 8,433)	(7,890 – 24,915)	(7,132 – 13,847)	(7,858 – 14,698)	**0.008**†
Δ¶ in €	+355	+8,919	+2,573	-730	

Abbreviations: Lvm Low-value medications; PwD Persons with Dementia; HRQoL Health-Related Quality of Life; SF-12 Short Form Health Survey mental/physical dimension, range 0-100, higher score indicates better quality of life; SD standard deviation; CI confidence interval
*Differences in proportions: Kruskal-Wallis test
†Differences in means: oneway analysis of variance (ANOVA)
‡ difference between baseline and one year after
¶ difference between baseline and two years after
p values less than 0.05 are highlighted in bold § p < 0.1

4.2.4. Impact of low-value medications on PRO

Lvm (receipt vs. nonreceipt) had a significant, negative impact on patients' physical HRQoL (b=-1.55; 95% CI, -2.76 – -0.35; p=0.011), subsequently decrease more intensively the longer that the Lvm intake was. Compared to PwD who did not receive Lvm, continuous Lvm intake over 24 months caused a lower physical HRQoL (b=-3.35; 95% CI, -6.73 – -0.02; p=0.051) than patients receiving Lvm only once (b=-1.85; 95% CI, -3.47 – -0.24; p=0.024). Sensitivity analyses indicated that low-value antiphlogistics/analgesics (b=-3.41; 95% CI, -5.15 – -1.67; p<0.001) and sedatives/ hypnotics (b=-3.11; 95% CI, -5.42 – -0.80; p=0.008) significantly reduced patients' physical HRQoL. The impact of Lvm on patients' mental HRQoL was not statistically significant.

The likelihood of hospitalizations significantly increased for patients receiving Lvm (receipt vs. nonreceipt) (OR=1.49; 95% CI, 1.06–2.09 OR; p=0.011). According to the intensity of Lvm intake and compared to PwD not receiving Lvm, Lvm intake over one year had a significantly higher impact on hospitalization (OR=2.61; 95% CI, 1.22–5.56 OR; p=0.013) than in those receiving Lvm only once over 24 months (OR=1.61; 95% CI, 1.09–2.36 OR; p=0.016). Taking Lvm continuously over two years was not significantly associated with increased adjusted odds of hospitalization. The likelihood of hospitalization was significantly affected by low-value antipsychotics (see sensitivity analyses).

Lvm intake overall and once every 24 months increased medical health care costs (b=€6,810; 95% CI, -707–14,327; p=0.076; and b=8,421; 95% CI, €-69–€16,911; p=0.052; respectively) due to significantly higher hospitalization costs. Health care costs increased with a longer duration of Lvm intake (once: €8,421 over one year: €11,598; continuously over two years: €11,871). Sensitivity analyses confirmed that low-value antiphlogistics/analgesics (b=€10,282; 95% CI, 4,068–16,497; p=0.001) were the main cause of higher health care costs. Tables 12 and 13 summarize the results of the multiple regression and sensitivity analyses.

Table 12: Impact of Lvm on Quality of Life, Hospitalizations and Health Care Costs

	Treatment effect PwD receiving Lvm Yes			**Intensity of Lvm intake (cumulative effect) Once in 24 months**			**One year**			**Two years**		
Outcome variable	**b**	**95% CI**	***p value***	**b**	**95% CI**	***p value***	**b**	**95% CI**	***p value***	**b**	**95% CI**	***p value***
Health-related quality of life												
Mental HRQoL (SF-12)	-0.38	-1.51 – 0.75	0.507	-0.33	-1.68 – 1.01	0.625	-0.61	-3.61 – 2.39	0.692	-0.07	-3.47 – 3.33	0.968
Physical HRQoL (SF-12)	-1.55	-2.76 – -0.35	**0.011**	-1.85	-3.47 – -0.24	**0.024**	-0.95	-3.71 – 1.80	0.498	-3.35	-6.73 – 0.02	0.051§
Hospitalization												
In-hospital treatment	1.49‡	1.06 – 2.09‡	**0.022**	1.61	1.09 – 2.36‡	**0.016**	2.61	1.22 – 5.56‡	**0.013**	1.60	0.65 – 3.95‡	0.309
Health care costs from payers' perspective†												
Medical care costs†	6,810	-707 – 14,327	0.076§	8,421	-69 – 16,911	0.052§	11,598	-11,371 – 34,566	0.322	11,871	-13,125 – 36,867	0.352
Physicians†	-37	-124 – 49	0.399	0.3	-87 – 88	0.995	-53	-401 – 295	0.765	37	-308 – 382.1	0.832
In-hospital†	6,953	-546 – 14,451	0.069§	7,893	-762 – 16,549	0.074§	11,067	-11,046 – 33,180	0.327	10,832	-13646 – 35,310	0.386
Medications†	-227	-496 – 41	0.097§	268	-32 – 567	0.080§	59	-840 – 958	0.897	449	-576 – 1,475	0.390
Medical aids†	-5	-182 – 172	0.955	-69	-201 – 64	0.311	-48	-709 – 613	0.886	-58	-781 – 665	0.876
Therapies†	101	-37 – 238	0.152	112	-15 – 239	0.083§	-28	-292 – 235	0.832	188	-180 – 556	0.317

Abbreviations: *Lvm* Low-value medications; *PwD* Persons with Dementia; HRQoL Health-Related Quality of Life; *SF-12* Short Form Health Survey mental/physical dimension, range 0-100, higher score indicates better quality of life; b observed coefficient; CI confidence interval *Multiple panel data regression models; standard errors were estimated with a nonparametric bootstrapping (2,000 replications) Models were adjusted for socio-demographic and clinical variables: age, sex, dementia diagnosis (ICD-10: F00, F01, F02, F03, G30), functional impairment (B-ADL), depression (GDS), comorbidities (CCI), number of ICD-10 diagnoses, polypharmacy (≥ 5 prescribed medications), number of potential drug interactions, the respective baseline outcome values and a lagged Lvm variable †Difference between baseline and two years after ‡Odds ratio (95% CI) p values less than 0.05 are highlighted in bold § $P < 0.1$

Table 13: Sensitivity analyses – Impact of Lvm clusters on Quality of Life, Hospitalizations and Health care Costs*

	Treatment effect of Low-value: Antiphlogistics/ analgesics			**Antidementia drug treatments**			**Sedatives/ hypnotics**		
Outcome variable	**b**	**(95% CI)**	***p value***	**b**	**(95% CI)**	***p value***	**b**	**(95% CI)**	***p value***
Health-related quality of life									
Mental HRQoL (SF-12)	0.07	-1.56 – 1.71	0.930	1.07	-0.83 – 2.96	0.269	-1.03	-3.20 – 1.13	0.348
Physical HRQoL (SF-12)	**-3.41**	**-5.15 – -1.67**	**< 0.001**	-0.31	-2.30 – 1.68	0.760	**-3.11**	**-5.42 – -0.80**	**0.008**
Hospitalization									
In-hospital treatment	0.93‡	0.56 – 1.53‡	0.772	1.09‡	0.61 – 1.96‡	0.764	1.00‡	0.52 – 1.95‡	0.995
Health care costs from payers' perspective†									
Medical care costs†	**10,282**	**4,068 – 16,497**	**0.001**	-3	-7,121 – 7,114	0.999	-3,198	-11,646 – 5,251	0.458
Physicians†	17	-112 – 146	0.799	42	-103 – 188	0.570	13	-160 – 187	0.882
In-hospital†	**10,400**	**4,307 – 16,494**	**0.001**	379	-6,605 – 7,362	0.915	-3,677	-11,982 – 4,628	0.386
Medications†	**-373**	**-717 – -30**	**0.033**	-173	-557 – 211	0.376	-74	-538 – 390	0.756
Medical aids†	39	-167 – 246	0.708	-37	-270 – 196	0.755	-181	-458 – 96	0.200
Therapies†	53	-118 – 223	0.547	-80	-273 – 112	0.413	144	-84 – 372	0.217

Abbreviations: *Lvm* Low-value medications; *PwD* Persons with Dementia; HRQoL Health-Related Quality of Life; *SF-12* Short Form Health Survey mental/physical dimension, range 0-100, higher score indicates better quality of life; b observed coefficient; CI confidence interval *Multiple panel data regression models; Models were adjusted for socio-demographic and clinical variables: age, sex, dementia diagnosis (ICD-10: F00, F01, F02, F03, G30), functional impairment (B-ADL), depression (GDS), comorbidities (CCI), number of ICD-10 diagnoses, polypharmacy (≥ 5 prescribed medications), number of potential drug interactions, the respective baseline outcome values and a lagged Lvm variable †difference between baseline and two years after ‡Odds ratio (95% CI) p values less than 0.05 are highlighted in bold § $P < 0.1$

Continued Table 13: Sensitivity analyses – Impact of Lvm clusters on Quality of Life, Hospitalizations and Health Care Costs*

	Treatment effect of Low-value: Antidepressants			Antipsychotics		
Outcome variable	**b**	**(95% CI)**	***p value***	**b**	**(95% CI)**	***p value***
Health-related quality of life						
Mental HRQoL (SF-12)	-2.29	-5.00 – 0.41	0.097§	-0.36	-2.91 – 2.19	0.779
Physical HRQoL (SF-12)	1.17	-1.81 – 4.14	0.442	0.66	-2.19 – 3.50	0.651
Hospitalization						
In-hospital treatment	1.73‡	0.79 – 3.81‡	0.173	**2.94‡**	**1.43 – 6.07‡**	**0.004**
Health care costs from payers' perspective†						
Medical care costs†	599	-9,104 – 10,301	0.904	8,980	-1,712 – 19,672	0.100
Physicians†	82	-115 – 279	0.414	-80	-296 135	0.465
In-hospital†	1,063	-8,460 – 10,586	0.827	8,893	-1,593 – 19,380	0.096§
Medications†	-146	-670 – 378	0.584	-25	-602 – 553	0.933
Medical aids†	-91	-408 – 226	0.574	303	-51 – 656	0.093§
Therapies†	-172	-434 – 90	0.197	-114	-404 – 176	0.440

Abbreviations: *Lvm* Low-value medications; *PwD* Persons with Dementia; HRQoL Health-Related Quality of Life; *SF-12* Short Form Health Survey mental/physical dimension, range 0-100, higher score indicates better quality of life; b observed coefficient; CI confidence interval *Multiple panel data regression models; Models were adjusted for socio-demographic and clinical variables: age, sex, dementia diagnosis (ICD-10: F00, F01, F02, F03, G30), functional impairment (B-ADL), depression (GDS), comorbidities (CCI), number of ICD-10 diagnoses, polypharmacy (≥ 5 prescribed medications), number of potential drug interactions, the respective baseline outcome values and a lagged Lvm variable †difference between baseline and two years after ‡Odds ratio (95% CI) p values less than 0.05 are highlighted in bold § *P*= < 0.1

5. Discussion

This section first discusses the analysis results against the background of previously published studies. The findings are then placed in a broader context, whereas the implications for the German health care system are discussed, aiming to reduce low-value services in dementia care.

5.1. Prevalence and impact of low-value medications

Concerning the research questions underlying this work, the prevalence over the stated study period of 24 months and the impact of low-value medications on health-related quality of life, hospitalizations, and health care costs will be particularly discussed, comparing the results with previously published national and international scientific contributions.

5.1.1. Prevalence of Low-value medications

The decreasing prevalence of PwD receiving Lvm over time aligns with previous findings presenting a decreasing prevalence over time [139, 140]. Given the potential harm of Lvm, this overall decrease over time could be explained by patients' perceived impairments in physical functioning, such as frequent falls. Otherwise, the increased risk of hospitalization could also be perceived by physicians reevaluating prescribed medications after the increased switch between outpatient and inpatient care.

However, the findings also indicate that over the entire observation period, more than one in two PwD received Lvm at least once. Especially international studies traced back low-value prescribing to a lack of time, misaligned reimbursement system incentives, distorted expectations of the relationship between patients and physicians, and incorrect perceptions of the harm and benefits of interventions [81-85]. Strategies to reduce Lvm in particular and low-value services, in general, must consider all these multiple factors in terms of structures, processes and paradigms, which amounts to a macro innovation for the health care system [141].

5.1.2. Impact on health-related quality of life

To address the full spectrum of harm, the present longitudinal analyses, as suggested by Korenstein et al. [86, 87], provide evidence of the harmfulness of Lvm at the individual patient level and confirm the negative effects of Lvm on physical HRQoL, extending previous cross-sectional findings [142]. The effect of decreasing patients' physical HRQoL was greater when the Lvm were taken and even strengthened with increased duration. A retrospective cohort study in PwD demonstrated that each additional drug increased the risk of adverse outcomes, such as mortality or hospitalization, which is also associated with consequences for HRQoL [118]. While the number of drugs remained constant for PwD without Lvm, among those with Lvm, it increased on average by one after 24 months.

However, Lvm themselves could drive the effect. Antipsychotics and benzodiazepines accounted for 32% of the captured Lvm in this study. Previous studies have underscored especially the increased risk of falls and, thus, the risk of hospitalizations associated with antipsychotics and benzodiazepines among PwD, which could affect self-perceived health [143, 144]. The sensitivity analyses support these findings, indicating significantly lower physical HRQoL caused by sedatives and hypnotics, including benzodiazepines, and an increased hospitalization risk due to low-value antipsychotics. Our findings suggest a requirement of close patient monitoring by primary care physicians if Lvm are prescribed due to their shortened scope of action as second-line therapies.

5.1.3. Impact on hospitalizations

Heider et al. [145, 146] already emphasized PIM's health economic relevance in aged individuals due to increased health resource utilization, particularly due to hospitalizations. The findings of the present analyses for Lvm in dementia are consistent with these studies. However, the increased hospitalization risk was higher for those who received Lvm for only one year (161%) than for PwD taking Lvm continuously over two years (60%). PwD who received Lvm continuously demonstrated the highest hospitalization rate (46%) at baseline with limited potential to increase, indicating saturation (ceiling) effects. While PwD with a continuous Lvm

intake showed this saturation, hospitalizations of those with short-term Lvm intake increased (receiving Lvm once: +77%; 12 months Lvm intake: +81%), confirming increased hospitalizations due to Lvm.

According to Badgery-Parker et al. [88] and Chalmers et al. [89], the increased hospitalization risk carries the potential for additional downstream low-value services that potentially cause further harm and consume resources needed for patients whose care would be more urgent. Hospitalizations always have implications for PwDs' quality of life, entailing adverse outcomes such as an increased risk for subsequent institutionalization [64]. The hospital admission reasons are less the dementia diagnosis but rather fractures, for instance [64, 66, 67]. Reducing low-value prescribing in dementia, especially benzodiazepines and antipsychotics, as elaborated above, could reduce the risk of falls, entailing fractures and related hospitalizations [143, 144]. Therefore, approaches need to be implemented at an earlier stage, i.e. in primary care, encouraging prescribers to avoid low-value care.

5.1.4. Impact on health care costs

The multiple regression analyses revealed that Lvm caused increased medical care costs longitudinally and thus confirmed several studies that indicated an association between health care costs and low-value prescribing in cross-section [25, 26]. This effect seemed primarily driven by PwD who received Lvm once during the 24 months (€8,421), while those continuously receiving Lvm showed no more significant changes (-730€ in 24 months) due to the aforementioned potential saturation (ceiling effect) already at baseline (€12,008). In particular, hospitals (€7,893) contributed to the additional costs.

Furthermore, Michalowsky et al. [19] show that functional impairment is a major driver of health care costs in PwD. Our analysis suggests that Lvm result in decreased HRQoL regarding the physical health state comprising physical functioning, which, in consequence, could further exacerbate cost pressure for health care payers beyond increased hospitalizations. Given the expected increasing numbers of PwD and the growing socioeconomic and financial burden on the health care system, the negative effects of Lvm on health economic outcomes emphasize the need for action to shift

spending to higher-value resource use [14, 16]. However, Pohl-Dernick et al. [147] calculated the health care costs for services identified as alternative high-value services to the Lvm in the PRISCUS list, concluding substantial additional costs entailing a lack of short-term incentives for payers. Further research must clarify whether potential savings in financial resources due to reduced hospital care could offset and justify the higher health care expenditures in primary care.

5.2. Implications for the health care system

The discussion of the results has shown that despite existing tools and initiatives to reduce low-value care, which indicate an awareness of the problem, the frequency of low-value care tends to decrease only slightly. However, given the expected increasing prevalence of PwD, preventable harm to patients and cost pressure for payers could be increased. Studies have already shown that incentives or nudging of providers alone are not enough. The reasons are multidimensional and of high complexity, and therefore, reform efforts, in sum, correspond to macro innovation in health care. The discipline of health economics is generally composed of four functions, comprising [1]:

1. the description,
2. the explanation,
3. the evaluation, and finally,
4. the derivation of recommendations for action to overcome the problem of scarce resources.

The following section focuses on the latter, particularly recommendations for reducing low-value medications derived from the present analyses' findings, distinguishing between the patient, provider, and payment levels considering the complexity of required actions.

5.2.1. Implications at the patient level

The patient level, including the physician-patient relationship, represents the micro-level comprising all the related structures, processes and paradigms [141]. Before the

question of suitable recommendations for action at the patient level can be answered, characteristics by which the patient level in the health care system is determined and the assumptions on which this is based will be briefly summarized.

In principle, individuals do not always make self-determined and rational decisions concerning their health, as decisions differ from classic consumer decisions due to the credence good nature of health services [32]. In addition, health care markets are characterized by imperfect information, which is reflected in information asymmetries, i.e., physicians, for example, have an information or knowledge advantage over patients due to their training [148, 149]. For this reason, the so-called principal-agent theory comes into play. Patients (principals) engage health service providers (agents) with confidence that they will act in the patient's best interests [148, 149]. However, physicians are agents in their own right, with their interests, values and goals, which is why deviations from optimal care can occur in practice, as in the case of so-called provider-induced demand [148, 149]. Based on the classic market model, where providers and consumers face each other, it is necessary to strengthen patient sovereignty analogous to consumer sovereignty.

Therefore, an important approach could be shared decision-making characterized by physicians involving patients. Given the basic problem of the principal-agent theory, it is, therefore, necessary to reduce the information gap. Some strategies, therefore, rely on patient education to establish an equal base [96]. However, this raises two challenges: 1) Are participatory forms of decision-making, such as shared decision-making for patients with cognitive impairments, such as PwD, an effective and thus realistic way to reduce low-value care? Furthermore, 2) Is not the information asymmetry in drug care too great, and are patients without a certain level of prior knowledge thus unable to adequately assess treatment quality?

Regarding the first question, some approaches suggest that low-value care on the patient's level is primarily unwanted care, and to avoid this, clinicians should primarily listen to PwD, regardless of whether patients have previously undergone patient education measures or not, since patients know best what they want [37]. For example, patients receive life-prolonging measures, although they prefer palliative care or reject treatments due to religious convictions [37]. However, this assumes that PwD know

their preferences and wishes. Accordingly, studies show that PwD can express preferences and even weigh them with support [150, 151]. Furthermore, family caregivers could also be more involved, if any are available. Usually, they are closest to patients and can be considered trustees of their interests. However, they also have their own needs and interests, which must be considered [152, 153]. Nevertheless, depriving PwD of the process of joint decision-making from the outset is to be denied.

Regarding the second question: Information asymmetry is particularly high in drug care, and some barriers should be considered regarding projects aimed at de-implementation. According to Augustson et al. [154], the patient level is associated with various barriers, which are expressed in resistance to projects aiming at de-implementation or in the demands of patients for certain services. This perspective is supported by Norton and Chambers [91], who emphasize that several patient-level factors should be priced in for strategies to be effective. These include, for example, fear of delayed diagnosis, outdated value patterns such as the conviction that more (or new) treatments are always better than less (or conventional) treatments, and a potential loss of trust in the physician-patient relationship due to the feeling that something is to be taken away from them [91]. Furthermore, according to Hoffmann et al. [83], patients usually overestimate the benefits of the intervention and underestimate the harms.

In addition, little is known about the factors that influence the value of a medication from a patient's perspective. A qualitative study with community-dwelling adults older than 65 by Pickering et al. [155] showed that four factors, in particular, determine the value of drug care from the patient's perspective:

1. perceived effectiveness,
2. negative impact on quality of life,
3. health care costs, and
4. a close physician-patient relationship.

From this, older patients may have a perception of medication care quality that treating physicians can incorporate to enforce goals such as deprescribing in routine care, even in the face of the potential patient resistance outlined above.

Despite potential barriers and attitudes at the patient level, the recommendation for action or implication that arises for stakeholders and decision-makers in the health care system aims to strengthen the role of patients as the starting point of all actions, to focus on their needs and preferences, and ultimately to realize so-called patient-centred care. The production of health services can only take place together with the patient. Patients are both a production factor and a judge of whether the function of producing health has been fulfilled. Patient-centred care also corresponds to the system model of producing health services. However, it requires time spent by health care providers during the health service provision. For example, Roßmeier et al. [80] show that deprescribing antipsychotics to PwD is a multi-step and multi-month process. Even if it sounds like a truism, starting from the status quo, this challenge must be organized and especially financed. Particularly because a shortage of GPs in rural areas and a shortage of skilled nursing staff mean that fewer and fewer staff have to treat or care for more and more patients in the same amount of time. Nevertheless, further research must examine low-threshold opportunities to express and assess medications' perceived effectiveness and potential harms by PwD, their family caregivers, or other proxy stakeholders.

5.2.2. Implications at the provider or organizational level

The following implications and recommendations for avoiding low-value care in dementia care concern the meso-level, i.e. all structures, processes and paradigms from stakeholders of the entire health sector and address the overarching question of how society must organize its health care system to achieve this goal [141]. The following section will describe the prerequisites for the German health care system in terms of organization and division of labour needed to improve health care quality, with patient-centred care as the starting point.

Although it may seem trivial initially, person- or population-centred care presents a particular challenge because the German health care system is traditionally divided into an outpatient and an inpatient sector. Moreover, this sectoral division of labour is currently characterized by strong competition, which leads to inefficient outcomes between sectors (outpatient vs. inpatient) and within a sector (general practitioner vs.

specialist) [156, 157]. Already in 2009, the German Advisory Council on the Assessment of Developments in the Health Care System [157] emphasized in its annual report the need for a changed division of labour in the German health care system, which is still more oriented toward the acute care of individual diseases than toward the needs of increasingly chronically ill and multimorbid patients. The core elements here included are:

1. primary care oriented toward the gatekeeper system,
2. reorganizing secondary specialist care as an interface between outpatient and inpatient care, and
3. cooperation among all stakeholders involved in health care, especially between physicians and nursing.

Corresponding to the Advisory Council, Figure 16 compares sectoral and population-oriented care graphically.

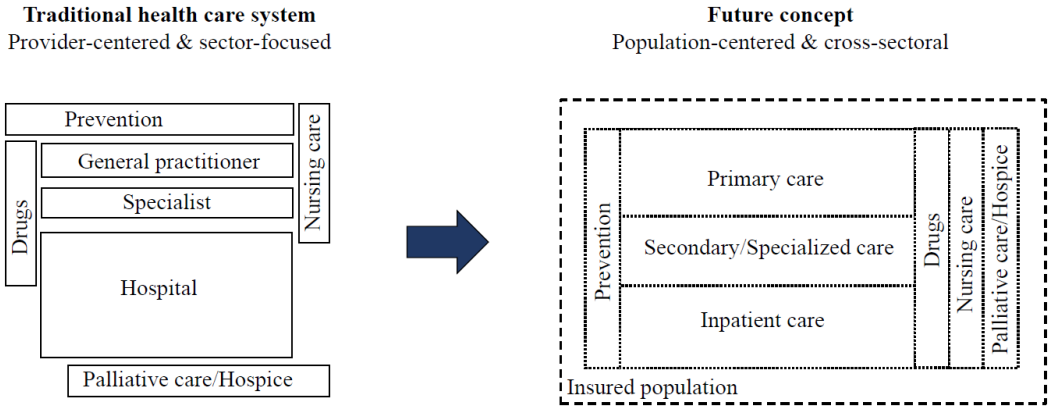


Figure 16: From sectoral to population-oriented care: Sectoral delimitation loses importance & regional structures decide where services are provided

Source: Own figure based on the German Advisory Council on the Assessment of Developments in the Health Care System [154]

The latter point will be discussed in more detail, aimed at more intensive cooperation between the service providers in the respective sectors. For this purpose, the concept of cooperation will first be clarified. A distinction is made between horizontal, vertical and lateral cooperation. Horizontal cooperation covers service providers in the same sector or production stage, vertical cooperation describes the relationship between service providers in upstream and downstream production stages, and lateral

cooperation is understood to mean cooperation across different production stages and sectors [32].

Sectorization of the health care system artificially interrupts the care pathway, favouring overuse and impeding treatment at the most cost-effective level of care [32]. Therefore, low-value care and entailing financial damage can also be regarded as interface costs. Especially through vertical cooperation, interdisciplinary and cross-sectoral collaboration could reduce costs and simultaneously improve the quality of care.

One appropriate form of vertical cooperation is disease management. In simple terms, this is a program for the coordinated treatment of disease from prevention to post-diagnostic or postoperative care [31]. It is particularly geared to chronic diseases since the various sub-processes of the care pathway, such as prevention, diagnostics, therapy or care, are distributed over a longer period among the different service providers in the respective sectors [32]. Care within disease management is evidence-based, following guidelines, and based on a standardized process with defined interfaces [31, 32]. The legislation defines which chronic diseases are to be made available as disease management based on the following criteria [31, 32, 156]:

1. a sufficiently high number of insured persons affected by the disease,
2. the possibility of improving care,
3. availability of evidence-based guidelines,
4. the need for treatment across sectors,
5. ability to influence the course of the disease through the insured person's initiative, and
6. the high financial cost of care.

Corresponding disease management for dementia has not yet been implemented in Germany. However, introducing so-called dementia care management is planned as part of the National Dementia Strategy [158]. Dementia care management is a cooperative model of dementia care, which specially qualified nursing professionals carry out, including a comprehensive baseline assessment first to record individual resources and needs at the medical, nursing, medication, psychosocial and socio-legal levels and subsequently to address these appropriately in close cooperation with the

treating GP [159, 160]. Dementia care management was evaluated regarding relevant patient- and care-related outcomes and was effective [113]. Likewise, cost-effectiveness was demonstrated [111]. Downstream studies are currently investigating how the activities of dementia care managers can be expanded in the context of task redistribution and in which health care setting it has the greatest benefit [161, 162]. Also, concerning Lvm, a recent study from the U.S. shows that collaborative dementia care significantly reduced PIM [163].

In order to improve vertical collaboration, further structural requirements are also necessary. Realizing the full potential of dementia care management depends on providing information, such as through access to information systems of practices and hospitals, interfaces to electronic patient records, and concerning Lvm, especially digitized medication plans. According to the recently published result report of the AdAM study [164, 165], an electronic medication management support system installed in GP practices using health insurance interfaces for claim data that provides previously unavailable treatment and care information to treating GPs can reduce mortality in Germany by 70,000 annually. In the case of low-value prescriptions, practice software could also integrate features such as directly reflecting potential harms to physicians by red flags, offering non-pharmacological alternatives and auto-defaults prescriptions to the lowest dose and number of pill days as aimed in a current study by Mafi et al. [166].

Beyond expanded access to care providers at the various stages of the care process, these digital interfaces could also expand the participation opportunities of patients or family caregivers as external production factors. Within the GAIN study [152], the unmet needs of family caregivers of PwD are assessed during the time spent in the waiting room, asking questionnaires usually not captured in routine care, indicating a perception of reduced waiting times and increased participation in the health service production for patients or caregivers while crucial information at the patient level for clinicians will be provided.

The recommendation for action resulting from this for the provider and organizational level is to intensify vertical cooperation and implement dementia-related disease management, such as dementia care management, as quickly as possible. The quality

dimensions described in 2.1.3.1 and shown in Figure 3 primarily concern changes in structural quality, i.e., personnel, material and organizational requirements. However, according to Donabedian's framework model, structural quality is a necessary but insufficient condition for process quality [32]. In other words, collaborative dementia care management is structurally necessary but insufficient to reduce low-value care and thus improve the quality of care for PwD. Therefore, also digital solutions must be implemented to support all processes aiming to reduce low-value care. For this purpose, further research is needed on interventions incorporating digital tools that enable information exchange between fragmented health sectors and between providers and patients, considering data assessments that are usually not recorded during routine care.

5.2.3. Implications at the payment level

The main management instruments for health care service provision beyond the organizational aspects comprise the payment of health care providers, including the design of insurance contracts. The last section focused primarily on organizational aspects, so the following section will examine aspects relevant to payment and health insurance.

Regarding the goal of containing low-value services, measures to limit the payment of low-value services are vital [167]. The so-called pay-for-performance model is the most prominent form of payment concerning quality-oriented reimbursement. Pay-for-performance is defined as a reimbursement system that focuses on the quality of providers, using external financial incentives to motivate providers to deliver higher-quality care and thus improve patient outcomes [168, 169]. The pay-for-performance model was thus intended as a corrective to other reimbursement forms, such as fee-for-services and flat rates per case, or to the disincentives resulting from them [169].

For implementing a payment model in the sense of the pay-for-performance approach, measurable quality indicators are both the primary prerequisite and, at the same time, the greatest challenge [168]. Therefore, clinical performance evaluation requires metrics that adequately map the care pathway along the three quality dimensions (structural, process, and outcome quality) and, thus, the production process of health

care services [44, 168]. However, despite clinical guidelines that can be used as a reference point for clinical metrics, the success of health care production depends primarily on external factors such as patient compliance or non-compliance [32, 168]. It follows that the incentives the pay-for-performance model provides are limited in effectiveness. Therefore, the degree of fulfillment to which the reimbursement should be oriented is also questionable.

The following possibilities exist to assess the degree of fulfillment [168]:

1. the absolute target achievement,
2. the relative achievement of targets,
3. the change compared to the previous period,
4. the comparison with a control group or
5. a combination of 1. – 4.

Empirically, the expected effects attributed to pay-for-performance models based on theoretical considerations could not be verified. In their systematic review of the effects of pay-for-performance in health care, Eijkenaar et al. [170] show that convincing evidence of cost-effectiveness is lacking, some studies did not find any effect, or the effect could not be distinguished from other measures. Schrappe and Gültekin [169] describe that pay-for-performance approaches in the medium and long term reveals so-called ceiling effects, entail partially reversible improvements that disappear when financial incentives are removed, and cause opportunity costs compared to non-incentivized care.

Nevertheless, elements of the pay-for-performance model should be given greater consideration, even if they are only applied subsidiarily in a multistage reimbursement process, to correct the misaligned incentives of the primary form of reimbursement [168]. Schrappe and Gültekin [169] also conclude that pay-for-performance models cannot be successful as a stand-alone instrument in the long term and must be further developed in the context of other quality-based care concepts. The authors see potential in the German health care system, particularly in the context of selective contracts in integrated care [169].

Integrated care is defined as care that is delivered as cross-sectoral or exclusively interdisciplinary care [31, 32]. It can be cross-indication or indication-related [32]. The central management instrument of integrated care is the so-called selective contract, which defines the cooperation between health insurance and service providers [32]. Health insurances negotiate selective contracts directly with all service providers, such as physicians, hospitals or nursing services, who act as joint partners [32]. The subject of the negotiations is supplementary contracts to the existing reimbursement for routine care, which has the advantage that, within the framework of selective contracting, reimbursement can be agreed upon outside the existing budgets [32]. At this point, for example, it would be possible to implement elements of quality-oriented payment.

The recommended course of action at the payment level to reduce low-value care is establishing conditions that favour an expansion of selective contracts, which have elements of pay-for-performance approaches. In addition, this may open up windows of opportunity for cross-sectoral care, requiring the control of patient and information flows according to management principles. The two previous sections explained how the requirements could be implemented organizationally and individually at the patient level. However, further research is needed to examine implementation barriers, promoting factors, and the effectiveness of low-value care reduction measures that link reimbursement and low-value care quality indicators.

5.3. Limitations

The present work has some limitations. Data were obtained in a rural area in northeastern Germany, potentially limiting the generalizability of the presented results. PwD with a higher functional impairment were more likely to drop-out due to death which may affect the generalizability of the presented findings for this population. Furthermore, patient-reported primary data were assessed by study nurses at patients' homes, possibly affecting their completeness and accuracy due to recall bias, especially for the assessed hospitalizations and health care costs. Additional claim data from health insurance or the possibility of linking primary and secondary data were unavailable. However, to minimize the recall bias, additional information about

medication use was obtained from treating practitioners, care providers, and caregivers in proxy interviews to increase the data validity and gain information about relevant clinical dimensions not usually available from secondary data. Additionally, the SF-12, a practical and adequate instrument for PwD with an MMSE score greater than 16, was used to assess HRQoL [128]. Thirty-six PwD with scores less than 16 at baseline were included, limiting the validity of the quantification of these endpoints. The sources for classifying medications as low-value represent expert consensus and predominantly emphasize clinical rationale, while the patient perspective, i.e. low-value care as adverse care, could not be included in the analyses. Finally, the PRISCUS List used to classify Lvm is an explicit tool offering practical advantages for large-scale epidemiologic studies due to its directly measuring the relevant data, albeit at the price of clinical contextual factors and individual patient needs [109, 171]. Thus, the prevalence of Lvm may have been overestimated since some prescriptions might have been classified as Lvm, although the health service provision was clinically adequate for certain reasons, illustrating a conflict regarding specificity and sensitivity, as described by Schwartz et al. [29].

6. Conclusion

This work aimed to determine the prevalence of PwD who received Lvm in dementia care and to demonstrate the impact of Lvm on patient-reported health economic outcomes in PwD. The following outcomes were considered for the analyses: HRQoL, hospitalizations, and direct medical costs from the payer's perspective.

In the first step, a cross-sectional analysis was performed to examine the associations between Lvm and the mentioned patient-reported and health economic outcomes. Subsequently, using panel-specific longitudinal analyses, we examined the change in the prevalence of Lvm over 24 months and their impact on patient-reported outcomes.

Both cross-sectional and longitudinal analyses relied on data from community-dwelling PwD from the DelpHi-MV study. Medications that were explicitly not recommended in dementia-specific guidelines, the German equivalent of the Choosing Wisely campaign, and negative lists such as the PRISCUS list were used to identify Lvm dichotomously (yes/no) as well as cumulatively (once, over one, or over two years).

The analyses showed that, on the one hand, the prevalence of Lvm decreased during the study period, but on the other hand, more than every second patient was affected in 24 months. In addition, Lvm were found to negatively impact patient-reported HRQoL, hospitalizations, and direct health care costs. While continuous use of Lvm had an increasingly negative impact on patients' HRQoL and showed saturation effects in hospitalizations and costs already at baseline, sporadic (one-time) or one-year use of Lvm was relevant for the further increase in hospitalizations and costs.

Appropriate alternative treatments are needed as early as possible in the patient journey through the health system to avoid HRQoL-decreasing downstream effects for patients and resource-burdening impacts for health systems. To this end, innovative approaches are needed to address the patient, provider, organizational, and payment levels, representing a macro innovation for German health care.

At the patient level, the patient is authoritative. Measures are needed to strengthen the role in shared decision-making, focus on his or her needs and preferences, and ultimately ensure patient-centred dementia care that, in addition, meets patient

expectations for pharmaceutical care. Since the care pathway in the German health care system is artificially separated by sectoral separation, the organizational conditions for stronger vertical cooperation must be created at the provider level. Dementia care management is a potentially cross-sector solution that has already proven cost-effective and has the potential to optimize medication use in PwD. Furthermore, the collaborative care process must be accompanied by digital solutions using interfaces for information exchanges of data routinely generated by all stakeholders in routine care and added by patients. However, conditions must be created beyond this via the payment level that develops incentives for the desired purpose. For example, options such as already implemented selective contracts can be expanded and supplemented with pay-for-performance elements.

Only through such a bundle of measures, as outlined above, can an allocation of scarce resources to efficient processes in the health care system be implemented and mitigate low-value care. Given the expected increase in PwD and the lack of a cure, avoiding Lvm and the whole spectrum of low-value services in dementia care is economically, politically and ultimately ethically imperative.

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Supplementary

Supplementary Table 1: Distribution of drop-outs due to reason "decease" according to Lvm intake

Lvm intake (baseline & follow-up 1)	**Mortality in the first 730 days**[†] **yes, n (%)**	**95%CI**	***p value****
No, n= 226 (53%)	36 (15.9)	(11.1 – 20.7)	0.363
Yes, n= 198 (47%)	26 (13.1)	(08.4 – 17.8)	

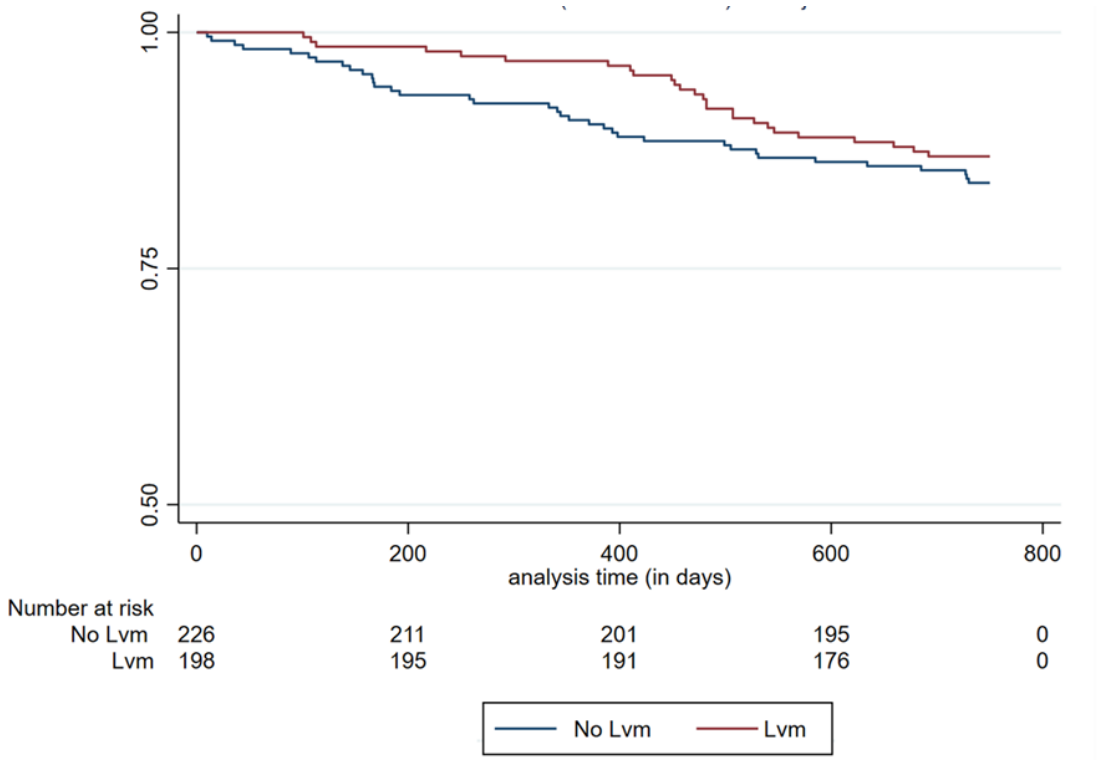
Abbreviations: Lvm, Low-value medications; CI confidence interval *Logrank test was used to assess the equality of the survivor functions. [†]10 Participants who died after 730 days were assessed as survivors

Supplementary Table 2: Hazard ratios (HR) for drop-outs due to death adjusted for multiple variables

	Multiple analysis			
N=424	**HR**	**SE**	**95% CI**	***p value***
Lvm before dead (Ref. yes)	0.83	0.22	0.49 – 1.40	0.480
Age	**1.05**	**0.02**	**1.01 – 1.10**	**0.029**
Sex (Ref. female)	0.69	0.18	0.41 – 1.16	0.163
Number of ICD-10 diagnoses	**0.96**	**0.02**	**0.92 – 1.00**	**0.031**
Polypharmacy (Ref. yes)	1.07	0.36	0.55 – 2.09	0.850
Number of drug interactions	1.13	0.15	0.87 – 1.47	0.371
Study group (Ref. controls)	1.56	0.42	0.92 – 2.66	0.100

Abbreviations: ICD International Statistical Classification of Diseases; Lvm Low-value medications; CI confidence interval; SE standard error

Supplementary Figure 1: Drop-out survival functions (Lvm vs. no Lvm) unadjusted



Supplementary Table 3: Sensitivity analysis of Lvm prevalence by intervention and control group

PwD receiving Lvm at	**Intervention group, n=254**	**Control group, n=98**	***p value****
Baseline, yes %	37.01	32.65	0.460*
95%CI	(31.05 – 42.97)	(23.34 – 41.97)	
After 12 mo, yes %	36.61	27.55	0.132*
95%CI	(30.67 – 42.56)	(18.67 – 36.43)	
After 24 mo, yes %	31.50	22.45	0.115*
95%CI	(25.76 – 37.23)	(14.16 – 30.74)	

Abbreviations: Lvm, Low-value medications; PwD, Persons with Dementia; CI confidence interval *Differences in proportions: Fisher's exact Tests

Supplementary Table 4: Sensitivity analysis of main outcomes by intervention and control group*

Outcome variable	Treatment effect of Low-value: Intervention group (n=254) PwD receiving Lvm (ref. yes) b	(95% CI)	*p value*	Control group (n=98) PwD receiving Lvm (ref. yes) b	(95% CI)	*p value*
Health-related quality of life						
Mental HRQoL (SF-12-MCS)	-0.24	-1.57 – 1.10	0.728	-1.06	-3.09 – 0.96	0.303
Physical HRQoL (SF-12-PCS)	-1.73	-3.04 – -0.42	**0.009**	-1.41	-4.21 – 1.38	0.322
Hospitalization						
In-hospital treatment	1.51†	1.04 – 2.18†	**0.028**	1.69†	0.78 – 3.64†	0.182
Health care costs from payers' perspective†						
Medical care costs†	2,682	-919 – 6,283	0.144	7,831	-11,297 – 26,959	0.422

Abbreviations: *Lvm* Low-value medications; *PwD* Persons with Dementia; HRQoL Health-Related Quality of Life; *SF-12* Short Form Health Survey mental/physical dimension, range 0-100, higher score indicates better quality of life; b observed coefficient; CI confidence interval *Multiple panel data regression models; Models were adjusted for socio-demographic and clinical variables: age, sex, dementia diagnosis (ICD-10: F00, F01, F02, F03, G30), functional impairment (B-ADL), depression (GDS), comorbidities (CCI), number of ICD-10 diagnoses, polypharmacy (≥ 5 prescribed medications), number of potential drug interactions, the respective baseline outcome values and a lagged Lvm variable †difference between baseline and two years after ‡Odds ratio (95% CI) p values less than 0.05 are highlighted in bold § $P = < 0.1$

Articel 1: Prevalence of Low-Value Care and Its Associations with Patient-Centered Outcomes in Dementia

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Prevalence of Low-Value Care and Its Associations with Patient-Centered Outcomes in Dementia

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Abstract.
Background: Low-value care (LvC) is defined as care unlikely to provide a benefit to the patient regarding the patient's preferences, potential harms, costs, or available alternatives. Avoiding LvC and promoting recommended evidence-based treatments, referred to as high-value care (HvC), could improve patient-reported outcomes for people living with dementia (PwD).
Objective: This study aims to determine the prevalence of LvC and HvC in dementia and the associations of LvC and HvC with patients' quality of life and hospitalization.
Methods: The analysis was based on data of the DelpHi trial and included 516 PwD. Dementia-specific guidelines, the "Choosing Wisely" campaign and the PRISCUS list were used to indicate LvC and HvC treatments, resulting in 347 LvC and HvC related recommendations. Of these, 77 recommendations (51 for LvC, 26 for HvC) were measured within the DelpHi-trial and finally used for this analysis. The association of LvC and HvC treatments with PwD health-related quality of life (HRQoL) and hospitalization was assessed using multiple regression models.
Results: LvC was highly prevalent in PwD (31%). PwD receiving LvC had a significantly lower quality of life ($b = -0.07$; 95% CI –0.14– –0.01) and were significantly more likely to be hospitalized (OR = 2.06; 95% CI 1.26–3.39). Different HvC treatments were associated with both positive and negative changes in HRQoL.
Conclusion: LvC could cause adverse outcomes and should be identified as early as possible and tried to be replaced. Future research should examine innovative models of care or treatment pathways supporting the identification and replacement of LvC in dementia.

Keywords: Alzheimer's disease, health-related quality of life, hospitalization, low-value care, patient-centered outcomes

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INTRODUCTION

Population aging is one of the challenges health systems face globally. This is associated with an increase in the prevalence of people suffering from dementia [1]. The World Alzheimer Report 2019 estimated that more than 50 million people live with dementia (PwD) worldwide. Within the next 30 years, the number of patients is predicted to reach 152 million, representing a considerable societal and economic burden [2]. The cost of dementia is estimated to be over US$1 trillion worldwide, and this figure could double by 2030 [2, 3].

Rapidly increasing healthcare expenditures are likewise a global problem. While most of these expenditures are caused by demographic changes, new treatment possibilities, and increasing demand, Shrank et al. [4] estimated that the total annual costs of waste were $760 billion to $935 billion, representing 25% of total healthcare spending. Wasted health expenditures are mainly driven by failures in care delivery and coordination, pricing failures, fraud, abuse, and also overtreatment, as well as low-value care (LvC) defined as care unlikely to provide a benefit to the patient regarding the patient's preferences, potential harms, costs, or available alternatives [5–7]. The study of Shrank et al. [4] revealed that LvC caused $75.7 to $101.2 billion annually in the US.

Overdiagnosis and overtreatment, as well as overtesting, and LvC are overlapping concepts addressing medical overuse along the entire care pathway [8]. As Elsaugh et al. [6] pointed out, freeing resources devoted to LvC could satisfy unmet health needs within the same budget. Related evidence gaps have been addressed in the research agenda for medical overuse [9]. Accordingly, evidence for effects and potential harms at the patient level is needed. Previous LvC-related studies have focused mainly on tests or nondrug procedures, using routinely collected data that represent the clinician's perspective [10, 11]. Concerning drug treatments, this approach covers prescribing behavior, but findings addressing downstream patient-level effects of these low-value prescribing practices are rare.

In contrast, high-value care (HvC) provides a benefit under consideration of all the mentioned aspects that define LvC [12]. However, it is difficult to distinguish between inappropriate and adequate health care service provision [13]. For this purpose, guidelines are providing support by issuing recommendations for or against health services representing over- and underuse or already established concepts by listing potentially inadequate medication [14–16].

PwD are a vulnerable multimorbid population that needs to receive HvC to delay the progression of cognitive decline, increase or maintain health-related quality of life (HRQoL) and live as long as possible community dwelling [17–19]. However, studies have revealed that PwD rarely receive evidence-based treatment and care according to guidelines [20]. Only 39% of people with positive dementia screening in primary care received a formal diagnosis at all, only 30% of PwD were provided with anti-dementia drugs, and 36% were provided with nondrug therapies, as recommended by guidelines [21–24]. Additionally, Amann et al. [25] showed that up to a quarter of elderly individuals receive potentially inadequate drugs. A recent study has shown that 93%of PwD had at least one drug-related problem, representing one part of LvC, which further leads to increased healthcare cost [26]. It is known that for elderly individuals and PwD, the likelihood of receiving LvC increases with age, higher comorbidity, and higher deficits in their daily living [11, 27].

Reducing LvC could simultaneously lead to greater efficiency in the healthcare system and higher value for patient-centered outcomes [28]. However, a recent survey with general practitioners (GPs) revealed that LvC is highly present in routine care [29]. The increasing number of PwD and the associated increasing socioeconomic burden of disease lead to a need to identify and replace LvC within routine care efficiently.

Previous research on LvC in dementia has focused on the frequency and its associated sociodemographic and clinical factors, as well as on its potential reduction [11, 27, 30]. Studies that consider both LvC and HvC at the same time to examine their respective associations with patient-reported outcomes, such as quality of life, or data, such as hospitalizations, are currently missing. Therefore, this study aims to demonstrate the prevalence of LvC and HvC treatments as well as to examine the associations between LvC and HvC treatments and patient-centered outcomes using data on community-dwelling PwD.

MATERIALS METHODS

The DelpHi-trial

Design and participant flow

The cross-sectional analysis used the baseline data of the cluster-randomized, controlled interventional

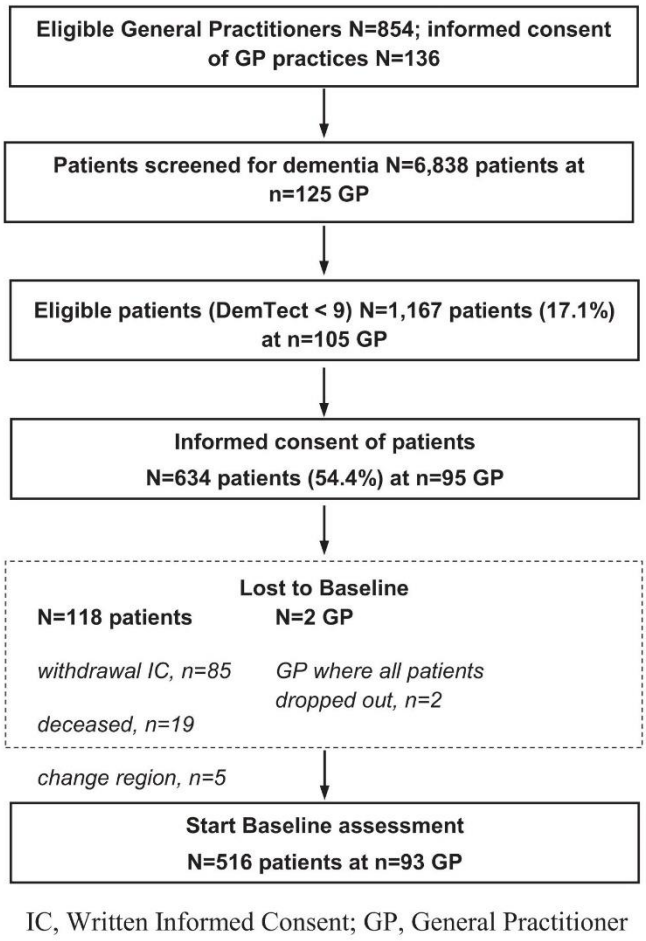


Fig. 1. DelpHi-trial flowchart.

DelpHi trial [31]. A total of 125 GP practices in Mecklenburg-Western Pomerania (state of Germany) screened 6,838 patients (≥ 70 years, living at home) for dementia using the short interview-based DemTect procedure [32], which is more suitable and sensitive than the Mini-Mental State Examination [33] to detect early stages of dementia [34]. The eligibility criteria (DemTect < 9) were met by a total of 1,166 (17%) patients who were subsequently informed about the study by the GP and asked for written informed consent. In total, 634 (54%) persons agreed to participate in the trial. Of these, 516 patients completed the baseline assessment, representing the data basis of this analysis. The Ethics Committee of the Chamber of Physicians of Mecklenburg-Western Pomerania approved both the study protocol and documents for written IC (registry number BB 20/11). The design of the trial can be found in the study protocol [31]. Figure 1 shows the flow chart of the study up to the baseline assessment.

Sociodemographic and clinical data

Sociodemographic data (age, sex) and the following clinical variables were assessed within the baseline assessment carried out by dementia-specific qualified nurses, so-called dementia care managers: cognitive impairment according to the Mini-Mental State Examination (MMSE) [33], comorbidity according to the number of ICD-10 (International Statistical Classification of Diseases and Related Health Problems, 10th revision) diagnoses listed in the GP files [35], depression symptoms according to the Geriatric Depression Scale (GDS) [36] and deficits in daily living activities according to the Bayer Activities of Daily Living Scale (B-ADL) [37].

Patient-reported outcomes and data measures

HRQoL was assessed using the Quality of Life-AD (QoL-AD) [38] and the 12-Item Short-Form Health Survey (SF-12) [39]. The dementia-specific QoL-AD is the most commonly used health-related quality of life questionnaire in dementia with good psychometric properties [38]. The QoL-AD includes 13 items with a four-point Likert scale. The total score ranges between 13 and 52, indicating very low and very high HRQoL, respectively [19, 38]. The SF-12 is a generic, multidimensional instrument that measures the physical dimensions (SF-12-PCS) of HRQoL concerning the perception of general health, physical functioning, bodily pain, and role limitations due to the physical health state, as well as mental dimensions (SF-12-MCS) including social functioning, mental health, and vitality and role limitations due to emotional state [39]. The SF-12 is valid as a health status instrument in large community-based studies of older people and suitable for mildly to moderately cognitively impaired PwD [40, 41]. We further assessed patient hospitalization as patient-reported data in terms of whether the PwD had an acute or planned hospital stay (dichotomous: yes/no) within the last 12 months, using proxy ratings provided by caregivers to ensure the validity of the response [19].

Low- and high-value care measures

To indicate LvC and HvC treatments, the following three sources were used. We used the German "S3 guideline: Dementia" published by the German Association for Psychiatry, Psychotherapy and Psychosomatics and the German Society for Neuroscience, selecting treatments, procedures, and drugs that are effective, helpful, and highly recommended in their use (representing HvC) or should be omitted or avoided (representing LvC) [15]. Additionally, defined positive and negative recommendations of the international "Choosing Wisely" campaign were used to identify further LvC and HvC treatments [14]. Finally, we used the PRISCUS list, comprising a total of 83 substances of 18 drug classes that are potentially inadequate for older people. This list includes recommendations (LvC) and alternatives (HvC), representing a decision-making aid [16].

The recommendations in all three sources were reviewed by two and, in case of deviation, by three independent reviewers. The selection was made after a discussion according to these criteria: relevance, targeted audience, differentiation possibilities, and existence in the data set used for this analysis, according to previous studies [42]. A total of 270 (77.8%) out of 347 recommendations of the three independent sources had to be excluded because they did not meet the mentioned criteria (relevance (38.9%), targeted audience (1.4%), differentiation possibilities (19.6%), and data capture (17.9%)). Of the remaining 77 (22.2%) measurable recommendations, 51 (14.7%) recommendations could be assigned to LvC and 26 (7.5%) to HvC. Due to duplications and overlap, recommendations were broken down into individual components and grouped into measurable treatments, consistent with previous studies [10]. In conclusion, 14 measurable LvC and 11 measurable HvC treatments provided the basis for this analysis. The recommendations could also be divided into drug and nondrug recommendations. Following the PRISCUS list, the individual substances were grouped according to their drug classes. LvC treatments were completely drug-based, including a high proportion of inappropriate drugs. The selection process and all LvC and HvC measures are demonstrated in Supplementary Figure 1 and Table 2, respectively.

Statistical analysis

The study participants' sociodemographic and clinical characteristics and the prevalence of LvC and HvC treatments were presented using descriptive statistics. To identify patterns in clinical characteristics and to analyze the isolated effects of LvC and HvC on patient-reported outcomes, patients were categorized into the following groups: 1) receiving only HvC or 2) LvC, 3) both HvC and LvC, or 4) none of the measurable treatments. Differences between these respective treatment groups were assessed using *t*-tests, Fisher exact tests, Pearson's chi-squared test, and one-way analyses of variance

added by the Scheffé test. To assess the associations of LvC and HvC and patient-reported outcomes, multivariable regression models with random effects for the GP were fitted. Outcomes such as HRQoL (QoL-AD, SF-12-MCS, SF-12-PCS) and the probability of hospitalization (dichotomous: yes/no) were used as dependent variables, and LvC and HvC treatments were used as independent variables in separate models. To minimize confounding, models were adjusted for the following sociodemographic and clinical factors: age, sex, cognition (MMSE), functional impairment (B-ADL), and depression (GDS). In addition, Charlson Comorbidity Index (CCI) [43] diagnoses were included in the adjustment to consider the context in which treatments were prescribed. In separate models, LvC and HvC treatments were further summed dichotomously (no LvC/HvC versus at least one LvC/HvC) to assess the association of the overall LvC and HvC with the patient-reported outcomes. Linear regression models were used for metric patient-reported outcomes (HRQoL), and logistic regression models were used for dichotomous patient-reported data (hospitalization: yes/no). All statistical analyses were performed in STATA/IC 15 [44].

RESULTS

Sociodemographic and clinical characteristics

The study participants were on average 80 years old, mostly female, and were mildly cognitively and functionally impaired according to the MMSE and the B-ADL, respectively. There were no statistical differences between patients assessed at baseline ($n = 516$) and those who dropped out before follow-up ($n = 116$) in age, sex, and DemTect score. Regarding the subsamples, PwD who received only LvC and no HvC treatments had on average a significantly lower cognitive impairment according to the MMSE and lower functional impairment according to the B-ADL compared to PwD who received only HvC and no LvC treatments. There were no significant differences for any of the other variables. The sample characteristics are presented in Table 1.

Prevalence of low- and high-value care treatments

159 PwD (31%) received LvC treatments. These patients were more likely to be female (65% versus 35% male). Those who received only LvC treatments were significantly less cognitively and functionally impaired than PwD, who received only HvC, LvC and HvC, or neither treatment. A total of 79% of PwD ($n = 126$) received exactly one LvC treatment, and 21% ($n = 33$) received at least two. Approximately 73% of the LvC treatments ($n = 141$) concerned low-value antiphlogistics and analgesics, sedatives, and hypnotics as well as antidepressants and the use of memantine that does not comply with the guidelines.

In 194 PwD (38%), HvC treatments were present. PwD who received HvC treatments had, on average, significantly lower cognitive functions, more deficits in daily living activities, and a higher HRQoL than patients who received LvC alone or in addition. Seventy-four percent of PwD ($n = 144$) obtained exactly one HvC treatment, and 26% obtained at least two treatments ($n = 50$). A total of 72% of the recommended HvC treatments ($n = 188$) involve the use of high-value antiphlogistics and analgesics, antidementia drugs, antipsychotics, and antidepressants. Occupational therapy had the highest proportion of nondrug treatments among HvC therapies, at 5% ($n = 13$). Table 2 displays the frequency of the respective LvC and HvC treatments. Table 3 summarizes the findings for sex, means, and mean differences of clinical characteristics by treatment groups, and the frequencies per case are shown in Supplementary Table 1.

Associations between low- and high-value care treatments and patient-centered outcomes

The multivariate regression analyses revealed that PwD who received LvC treatments had a significantly lower HRQoL, represented by a lower QoL-AD score ($B = -0.07$; 95% CI –0.14–0.01). After analyzing the treatments separately, sedatives and hypnotics ($B = -0.19$; 95% CI –0.32–0.06), which include benzodiazepines such as diazepam, clobazam, and medazepam, were also associated with a significantly lower QoL-AD score. PwD who received the antidementia drug memantine were associated with a significantly higher HRQoL with both recommended ($B = 0.14$; 95% CI 0.01–0.27) and non-recommended ($B = 0.17$; 95% CI 0.01–0.32) use according to the guideline. However, findings varied by treatment in terms of mental and physical health status, represented by different SF-12 scores. PwD who received high-value antidepressants ($B = -4.74$; 95% CI –8.08–1.41) such as sertraline or mirtazapine and likewise those who received either inadequate or guideline-based antiphlogistic

Table 1
Socio-demographic and clinical characteristics of the total sample and subsamples

	Total sample $n = 516$	Subsample LvC* $n = 159$	Subsample HvC† $n = 194$	p
Age				
Mean (SD)	80.0 (5.5)	79.3 (5.5)	80.3 (5.4)	0.051‡
Range	70 – 100	70 – 96	70 – 94	
Sex, n (%)				
Female	307 (59.50)	104 (65.41)	124 (63.92)	0.527§
MMSE				
Mean (SD)	22.2 (5.4)	23.0 (4.4)	20.4 (5.8)	**0.001**‡
Range	3 – 30	8 – 30	5 – 30	
Severity of dementia, n (%)				
No hint for dementia	108 (22.69)	33 (21.02)	21 (11.29)	
Mild dementia	239 (50.21)	94 (59.87)	87 (46.77)	
Moderate dementia	107 (22.48)	27 (17.20)	62 (33.33)	
Severe dementia	22 (4.62)	3 (1.91)	16 (8.60)	
B-ADL				
Mean (SD)	3.70 (2.57)	3.55 (2.33)	4.59 (2.78)	**0.001**‡
Range	1 – 10	1 – 10	1 – 10	
GDS				
Mean (SD)	3.17 (2.46)	3.52 (2.80)	3.37 (2.48)	0.576‡
Range	0 – 14	0 – 14	0 – 12	
Number of ICD-10 diagnoses				
Mean (SD)	13.16 (7.75)	13.67 (7.27)	13.38 (7.83)	0.854‡
Range	1 – 58	3 – 36	1 – 36	
QoL-AD				
Mean (SD)	2.70 (0.58)	2.66 (0.57)	2.62 (0.71)	0.419‡
Range	0 – 3.62	0 – 3.62	0 – 3.54	
SF-12 (physical)				
Mean (SD)	41.81 (10.51)	39.85 (10.17)	40.78 (10.88)	0.453‡
Range	12.95 – 60.62	12.95 – 58.12	12.95 – 59.24	
SF-12 (mental)				
Mean (SD)	52.92 (9.88)	52.44 (11.26)	52.12 (10.27)	0.648‡
Range	17.57 – 72.08	17.57 – 72.08	17.57 – 72.08	

LvC, Low-value Care; HvC, High-value Care; MMSE, Mini-Mental State Examination, range 0–30, higher score indicates better cognitive function; B-ADL, Bayer-Activities of Daily Living Scale, range 0–10, lower score indicates better performance; GDS, Geriatric Depression Scale, sum score 0–15, score ≥ 6 indicates depression; ICD, International Statistical Classification of Diseases and Related Health Problems; QoL-AD, Quality of Life in Alzheimer's Diseases, mean sum score 1–4, higher score indicates better quality of life, SF-12, Short Form Health Survey, range 0–100, higher score indicates better quality of life; SD, standard deviation. *Patients received at least one LvC treatment. †Patients received at least one HvC treatment. ‡Differences in means: *T*-Test two-tailed referring to patients who received only LvC but no HvC or only HvC but no LvC. (overlaps were excluded). §Differences in proportions: Fisher's exact Tests referring to patients who received only LvC but no HvC or only HvC but no LvC. (overlaps were excluded).

or analgesic treatments ($B^{LvC} = -3.02$ versus $B^{HvC} = -3.02$) were associated with lower HRQoL.

Concerning hospitalization, receiving at least one LvC treatment was associated with significantly higher odds of hospitalization within the last 12 months (OR = 2.06; 95% CI 1.26–3.39). In particular, low-value antihypertensives drugs were associated with higher odds of hospitalization (OR = 4.18; 95% CI 1.19–14.65). Further, PwD treated with other low-value antidementia drugs such as piracetam were also more likely to be hospitalized (OR = 14.37; 95% CI 2.64–78.16). There was no significant association between receiving at least one HvC treatment or a certain HvC treatment and the patient-reported outcomes or hospitalization data of PwD. Table 4 and Fig. 2 show the results for associations between LvC and HvC and patient-centered outcomes of PwD.

DISCUSSION

This study aimed to examine the associations between LvC and HvC treatments and patient-reported outcomes and hospitalization data. One-third of community-dwelling PwD received LvC treatments,

Table 2
Frequency of LvC and HvC treatments

Low-value Care ($n = 194$) Treatment – Drug class (included substances)	n (%)	High-value Care ($n = 260$) Treatment – Drug class (included substances)	n (%)
Low-value antiphlogistics/ analgesics (Dexketoprofen, etoricoxib, indometacin, meloxicam, naproxen, diclofenac)	59 (30.41)	High-value antiphlogistics/ analgesics (Paracetamol, tramadol, codeine, ibuprofen)	62 (23.85)
Low-value Memantine does not complies with the guidelines for mild dementia	29 (14.95)	High-value other antidementia drugs (Donepezil, galantamine, rivastigmine)	51 (19.62)
Low-value sedatives/ hypnotics (Chloral hydrate, chlordiazepoxide, clobazam, diazepam, zopiclon, diphenhydramine, doxylamine, medazepam, nitrazepam, zolpidem)	28 (14.43)	High-value antipsychotics (Risperidone, melperone, pipamperone)	38 (14.62)
Low-value antidepressants (Amitriptyline, amitriptylinoxide, doxepin, trimipramine)	25 (12.89)	High-value antidepressants (Citalopram, escitalopram, sertraline, mirtazapine, opipramol)	37 (14.23)
Low-value antihypertensives (Clonidine, doxazosin, methyldopa)	16 (8.25)	High-value Memantine (complies with the guidelines for moderate to severe dementia)	29 (11.15)
Low-value spasmolytics (Solifenacin, tolterodine)	10 (5.15)	High-value occupational therapy (complies with the guidelines for mild to moderate dementia)	13 (5.00)
Low-value other antidementia drugs (Naftidrofuryl, piracetam, dihydroergotoxine)	8 (4.12)	High-value spasmolytics (Trospium)	13 (5.00)
Low-value antiarrhythmics (Acetyldigoxin, flecainide, sotalol)	4 (2.06)	High-value antiemetics (Domperidone, metoclopramide)	12 (4.62)
Low-value muscle relaxants (Baclofen, tetrazepam)	4 (2.06)	High-value muscle relaxants (Tolperisone, tizanidine)	2 (0.77)
Low-value antipsychotics (Levomepromazine, olanzapine, haloperidol)	4 (2.06)	High-value antiarrhythmics (Amiodarone)	2 (0.77)
Low-value antipsychotic (Quetiapin) (does not complies with the guidelines for agitation and aggression)	3 (1.55)	High-value psychotherapy (complies with the guidelines for depression)	1 (0.38)
Low-value antiemetics (Dimenhydrinate)	2 (1.03)		
Low-value ergotamine (Dihydroergocryptine)	1 (0.52)		
Low-value vitamin E	1 (0.52)		

LvC, Low-value Care; HvC, High-value Care.

Table 3
Sex, means, and mean differences of clinical characteristics by treatment groups

3.1 Sex and means of clinical characteristics by treatment groups

Sex and clinical characteristics	LvC* $n = 102$		HvC* $n = 137$		LvC & HvC† $n = 57$		neither LvC nor HvC† $n = 220$		p
Sex female, n (%)	60	(58.82)	80	(58.93)	44	(77.19)	123	(55.91)	**0.034**‡
MMSE, n, mean (SD)	101	23.62 (4.16)	127	19.71 (6.16)	54	21.94 (4.67)	187	23.10 (5.01)	**< 0.001**§
B-ADL, n, mean (SD)	100	2.99 (2.01)	131	4.60 (2.89)	55	4.56 (2.53)	214	3.27 (2.40)	**< 0.001**§
GDS, n, mean (SD)	101	3.35 (2.66)	126	3.17 (2.17)	55	3.84 (3.04)	210	2.91 (2.34)	0.075§
QoL-AD, n, mean (SD)	102	2.71 (0.45)	136	2.64 (0.70)	57	2.57 (0.73)	215	2.77 (0.49)	0.050§
SF-12 (physical), n, mean (SD)	93	41.41 (9.17)	115	42.44 (10.29)	49	36.87 (11.35)	200	42.84 (10.72)	**0.004**§

3.2 Mean differences for clinical characteristics between the respective treatment groups§

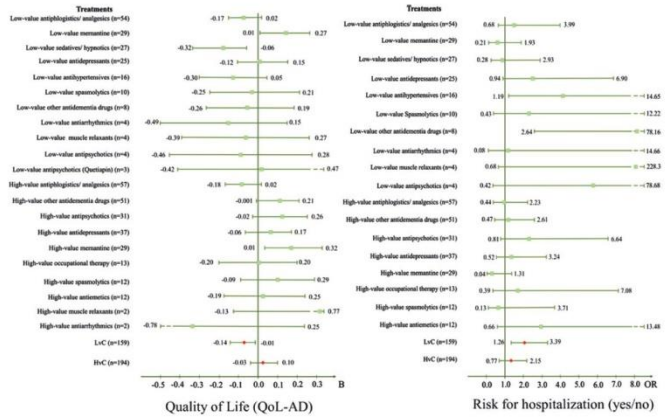
Patients receiving ... versus	Patients receiving ...	Mean difference (p *value*) MMSE	B-ADL	GDS	QoL-AD	SF-12 (physical)
only LvC	only HvC	**3.91 (0.000)**	**–1.61 (0.000)**	0.18 (0.960)	0.06 (0.867)	–1.03 (0.918)
	both LvC and HvC	1.68 (0.292)	**–1.57 (0.003)**	–0.49 (0.702)	0.14 (0.538)	4.54 (0.106)
	neither LvC nor HvC	0.53 (0.876)	–0.28 (0.827)	0.44 (0.540)	–0.07 (0.822)	–1.43(0.752)
only HvC	both LvC and HvC	–2.23 (0.071)	0.04 (1.000)	–0.67 (0.416)	0.08 (0.873)	**5.57 (0.020)**
	neither LvC nor HvC	**–3.38 (0.000)**	**1.32 (0.000)**	0.26 (0.834)	–0.13 (0.235)	–0.40 (0.991)
both LvC and HvC	neither LvC nor HvC	–1.15 (0.554)	**1.29 (0.009)**	0.93 (0.103)	–0.21 (0.124)	**–5.98 (0.005)**

LvC, Low-value Care; HvC, High-value Care; MMSE, Mini-Mental State Examination, range 0–30, higher score indicates better cognitive function; B-ADL, Bayer-Activities of Daily Living Scale, range 0–10, lower score indicates better performance; GDS, Geriatric Depression Scale, sum score 0–15, score ≥ 6 indicates depression; QoL-AD, Quality of Life in Alzheimer's Diseases, mean sum score 1–4, higher score indicates better quality of life, SF-12, Short Form Health Survey, range 0–100, higher score indicates better quality of life; SD, standard deviation. *Patients who received only LvC but no HvC or only HvC but no LvC. †Patients who received both LvC and HvC or neither HvC nor LvC. ‡Differences in proportions: Pearson's chi-squared test; §Differences in means: oneway analysis of variance (ANOVA) with a Scheffé *post hoc* test.

Table 4
Associations between LvC and HvC and patient-centered outcomes of PwD – HRQoL and Hospitalization

	QoL-AD (n = 450)		SF-12 Mental health (n = 417)		SF-12 Physical health (n = 417)		Hospital stay (n = 444)	
	B (SE)	CI$^{95\%}$	B (SE)	CI$^{95\%}$	B (SE)	CI$^{95\%}$	OR (SE)	CI$^{95\%}$
	Model I		Model III		Model V		Model VII	
Low-value Care								
Low-value antiphlogistics/analgesics*	−0.07 (0.05)	−0.17 0.02	0.69 (1.36)	−1.97 3.35	**−3.02 (1.41)***	**−5.77 −0.26**	1.43 (0.54)	0.68 2.99
Low-value Memantine*	**0.14 (0.07)***	**0.01 0.27**	2.25 (1.46)	−1.39 5.89	**3.85 (1.89)***	**0.14 7.55**	0.63 (0.26)	0.21 1.93
Low-value sedatives/ hypnotics*	**−0.19 (0.07)****	**−0.32 −0.06**	0.97 (1.88)	−2.72 4.66	−3.64 (1.93)	−7.41 0.13	0.91 (0.54)	0.28 2.93
Low-value antidepressants	0.01 (0.07)	−0.12 0.15	2.32 (2.00)	−1.59 6.23	−1.65 (2.07)	−5.70 2.40	2.55 (1.30)	0.94 6.90
Low-value antihypertensives*	−0.13 (0.09)	−0.30 0.05	−2.99 (2.51)	−7.91 1.92	1.09 (2.54)	−3.88 6.06	**4.18 (2.67)***	**1.19 14.65**
Low-value spasmolytics	−0.02 (0.12)	−0.25 0.21	2.25 (3.43)	−4.48 8.98	−3.93 (3.53)	−10.85 2.98	2.29 (1.96)	0.43 12.22
Low-value other antidementia drugs**	−0.04 (0.12)	−0.26 0.19	−6.63 (3.66)	−13.80 0.55	1.30 (3.73)	−6.01 8.61	**14.37 (12.42)****	**2.64 78.16**
Low-value antiarrhythmics	−0.17 (0.16)	−0.49 0.15	−4.32 (4.45)	−13.05 4.40	−1.93 (4.58)	−10.91 7.05	1.10 (1.45)	0.08 14.66
Low-value muscle relaxants	−0.06 (0.17)	−0.39 0.27	0.78 (4.49)	−8.03 9.59	−5.77 (4.69)	−14.97 3.42	12.48 (18.51)	0.68 228.3
Low-value antipsychotics	−0.09 (0.19)	−0.46 0.28	2.60 (5.00)	−7.20 12.05	−4.56 (5.33)	−15.00 5.88	5.74 (7.67)	0.42 78.68
Low-value antipsychotic (Quetiapin)	0.02 (0.23)	−0.42 0.47	−11.75 (6.27)	−24.03 0.54	−3.44 (6.36)	−15.90 9.03	– –	
High-value Care								
High-value antiphlogistics/analgesics**	−0.08 (0.05)	−0.18 0.02	0.94 (1.42)	−1.85 3.73	**−3.02 (1.45)****	**−5.87 −0.18**	0.99 (0.41)	0.44 2.23
High-value other antidementia drugs	0.11 (0.06)	−0.001 0.21	1.57 (1.64)	−1.63 4.78	2.39 (1.66)	−0.87 5.65	1.11 (0.49)	0.47 2.61
High-value antipsychotics	0.12 (0.07)	−0.02 0.26	−1.57(2.26)	−6.01 2.87	2.06 (2.32)	−2.49 6.61	2.31 (1.24)	0.81 6.64
High-value antidepressants**	0.06 (0.06)	−0.06 0.17	**−4.74 (1.70)****	**−8.08 −1.41**	1.03 (1.77)	−2.44 4.50	1.30 (0.61)	0.52 3.24
High-value Memantine*	**0.17 (0.08)***	**0.01 0.32**	−1.20 (2.36)	−5.83 3.43	1.92 (2.41)	−2.82 6.65	0.23 (0.20)	0.04 1.31
High-value occupational therapy	0.0003 (0.10)	−0.20 0.20	−0.98 (3.33)	−7.51 5.55	−1.39 (3.45)	−8.16 5.38	1.65 (1.23)	0.39 7.08
High-value spasmolytics**	0.10 (0.10)	−0.09 0.29	**8.29 (2.73)****	**2.94 13.64**	−0.08 (2.81)	−5.60 5.43	0.69 (0.59)	0.13 3.71
High-value antiemetics*	0.03 (0.11)	−0.19 0.25	−2.82 (3.16)	−9.01 3.37	**−6.87 (3.30)***	**−13.34 −0.39**	2.98 (2.30)	0.66 13.48
High-value muscle relaxants	0.32 (0.23)	−0.13 0.77	7.80 (6.15)	−4.25 19.85	−11.95 (6.48)	−24.65 0.76	– –	
High-value antiarrhythmics*	−0.32 (0.24)	−0.78 0.25	**−14.50 (6.39)***	**−27.03 −1.97**	−8.85 (6.63)	−21.84 4.14	– –	
R^2 overall	**0.46*****		**0.30*****		**0.36*****		*	
	Model II		Model IV		Model VI		Model VIII	
Aggregated Low- and High-value Care								
LvC	**−0.07 (0.03)***	**−0.14 −0.01**	0.12 (0.95)	−1.73 1.98	−1.58 (0.95)	−3.45 0.29	**2.06 (0.52)****	**1.26 3.39**
HvC	0.03 (0.03)	−0.03 0.10	−0.59 (0.95)	−2.46 1.28	−0.96 (0.97)	−2.86 0.95	1.29 (0.33)	0.77 2.15
R^2 overall	**0.42*****		**0.22*****		**0.31*****		***	

LvC: Low-value Care; HvC: High-value Care; PwD: People with Dementia; HRQoL: Health-Related Quality of Life; QoL-AD: Quality of Life in Alzheimer's Diseases, mean sum score 1–4, higher score indicates better quality of life; SF-12: Short Form Health Survey mental/physical dimension, range 0–100, higher score indicates better quality of life; OR: odds ratios; B: observed coefficient; SE: standard error; CI: confidence interval. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. The models used were adjusted for socio-demographic and clinical variables: age, sex, cognition (MMSE), functional impairment (B-ADL), depression (GDS), comorbidities (CCI).



LvC, Low-value Care; HvC, High-value Care; PwD, People with Dementia; HRQol, Health-Related Quality of Life; QoL-AD, Quality of Life in Alzheimer's Diseases, mean sum score 1-4, higher score indicates better quality of life; B, observed coefficient; OR, odds ratios

Fig. 2. Forest plots for the associations between LvC and HvC and patient-centered outcomes of PwD – QoL-AD and Hospitalization.

indicating that LvC was highly present in community-dwelling PwD. These patients were less functionally and cognitively impaired. LvC in PwD was mainly caused by drug therapies with low-value antiphlogistics and analgesics, sedatives, and hypnotics as well as antidepressants. Receiving at least one LvC treatment were associated with a lower HRQoL and an increased risk for hospitalization. HvC treatments were highly prevalent as well. However, the results show that recommended HvC services alone do not guarantee a positive patient-reported outcome. Whereas a guideline-based prescription of memantine was associated with an increased HRQoL, the recommended therapy alternatives with antidepressant drugs were associated with a lower HRQoL.

Several studies have already focused on various harmful treatments and their risk factors among PwD [11, 27]. According to these studies, the risk for receiving LvC is age-related and associated with a higher degree of comorbidity. In our data, there were no group differences in age and number of ICD-10 diagnoses between patients receiving only LvC or HvC treatments. However, it is already known that PwD have, on average, higher comorbidity than elderly individuals without dementia, underlining that PwD are a high-risk group for receiving LvC [45]. Contrary to previous routine data-based studies, the conducted patient-level analysis identifies that PwD who received LvC had fewer deficits in their activities of daily living and cognition than those who received HvC, indicating potentially less mental and physical comorbidities. On the other hand, in this study, patients were included after an initial screening procedure. At the time point of the screening, only 39% of patients had a formal dementia diagnosis [21]. This rate increased after the screening to 70% [46]. Hence, the systematic recruitment scheme increased the GPs' diagnostic attention, which may explain why our sample was less cognitively and functionally impaired than previous studies. Additionally, previous studies found that diagnosed cases were more often associated with severe MMSE scores and better anti-dementia drug treatment [21, 24], demonstrating earlier diagnosis could help to avoid LvC for PwD.

Considering HvC treatments, recent studies have shown that the probability of receiving care according to the guidelines for PwD depends on a patient's age, severity, and comorbidity, which is in line with the results of our study [22, 23]. PwD who received HvC treatments had lower cognitive functions and were slightly older, even though the age differences were not statistically significant. Lower HRQoL and greater deficits in activities of daily living also indicate a higher degree of comorbidity. However, in this study, there was no measured correlation between the comorbidity of PwD and the presence of the respective treatment group. In conclusion, further

studies are needed to evaluate the association of specific comorbidities and their respective single and combined impact on the presence of LvC and its downstream effects on patient-reported outcomes.

According to the research agenda on medical overuse [9], patient-level studies are needed to assess the harmful effects of overuse and to fill the research gap that results from studies based primarily on routine data. This conducted analysis revealed LvC could cause a lower HRQoL and is associated with a higher probability of hospitalization, providing findings of vital importance. The individual substance groups considered underscores these findings. The evidence for inappropriate antiphlogistics and analgesics show, there is no convincing evidence of efficacy against symptoms of Alzheimer's disease. Rather, these drugs are associated with an increased risk of gastrointestinal bleeding [15, 16]. Inappropriate sedatives and hypnotics are mainly benzodiazepines. Among elderly individuals, and particularly those with dementia, benzodiazepines are associated with higher risks of falls and fractures that cause hospitalizations [14]. Finally, also for antidepressants, especially those with anticholinergic properties, studies have already shown that their use is associated with an increased risk of hospitalization [47, 48]. Thus, our findings are in line with these studies.

Previous studies pointed out that the definitions of the respective LvC or HvC treatments vary in terms of specificity and sensitivity depending on the source used and the clinical context [13, 49]. Therapy alternatives with antidepressant drugs, such as sertraline or mirtazapine, are designated by the PRISCUS list [16]. The evidence, however, is still ambiguous. A study revealed no superiority of prescription of these antidepressant drugs over placebo but an association with adverse events [50]. Our findings were in line with this study, underlining the uncertainties associated with antidepressants in the treatment of PwD. Concerning memantine, guidelines recommend a treatment in moderate to severe dementia to improve cognition and everyday function but advise against it in mild dementia since efficacy is not proven and refer to alternatives [15]. The analyses performed show that memantine is associated with higher HRQoL in both cases, illustrating that LvC depends on the context and perspective from which it is defined. These findings emphasize that HvC is not the simple opposite of LvC and vice versa and that the expert perspective may differ from what the patient wants. The adoption of HvC needs to consider the clinical context and the organization of health care provision. Rather than focusing on the quality of single treatments, dementia care seems to require a more comprehensive disease management approach [51].

The care of PwD is high-value if it considers patient preferences and reduces the negative outcomes caused by LvC. Hence, dementia care should be addressed by innovative care models or treatment approaches, especially regarding hospitalization for PwD. Baicker and Chandra highlighted that hospitalizations are key drivers of health expenditures and that policy reforms should be guided by whether they improve the allocation of resources in care [52]. Recent studies have suggested comprehensive care models or treatment pathways to reduce the utilization of LvC in primary care as well as to improve patient-reported outcomes, claiming that these would simultaneously reduce health expenditures [17, 53, 54]. In times of increasing numbers of PwD and the growing socioeconomic burden on healthcare systems worldwide, innovative approaches and treatment strategies are of vital importance.

Cross-sectional data alone cannot establish cause and effect. It is possible that PwD with a lower HRQoL are treated with LvC; thus, HRQoL cannot be considered a consequence of the treatment. Further research should evaluate the observed associations of LvC and HvC with patient-reported outcomes in a longitudinal approach. There is also a need to identify relevant subgroups of PwD that could benefit most from canceling LvC treatments. We need to clarify whether the same subgroups or others would benefit the most from an increase in HvC, especially nondrug treatments.

Limitations

This cross-sectional analysis was based on the baseline data of the DelpHi trial [31]. The data represent a mainly rural region of Germany, which may limit the generalizability of the presented results to more urban settings. Primary data, especially on outcomes, were obtained directly from the patients. Other sources, such as health insurance, were not available [55]. Given the clinical course of dementia, the completeness and correctness of information may be affected by the limited cognitive capacities of the patients. However, the majority of patients in our sample had mild cognitive impairment or early-stage dementia. To increase the validity of our data, we systematically solicited further information from nursing services and caregivers [22]. The participants

of the study were on average 80 years old and were living community dwelling. Thus, we cannot generalize the findings to PwD living in institutions [26]. Additionally, the SF-12 is a practicable and adequate tool for assessing the HRQoL for PwD with an MMSE score greater than 16, but the study also included 40 PwD with a score less than 16, for whom the validity is restricted [17].

To directly measure LvC, clinical evidence-based guidelines and consensus-based expert publications were used, resulting in the following two limitations: First, the expert lens did not consider the patient perspective, such as LvC as unwanted care, and second, there is a lack of economic evidence in LvC recommendations, overemphasizing clinical rationales, as recently stated by Kim et al. [56]. Generally, the classification of treatment as LvC depends on the context of healthcare provision and, in particular, the diagnosis, which only 40% of PwD had at the time of the screening procedure before starting the baseline assessment. However, this proportion increased to 70% at the day of screening. Additional analyses revealed that the proportion of diagnosed PwD further increased the weeks after the screening procedure, still before starting the baseline assessment [21, 46]. Furthermore, the LvC-related findings are limited to drug-associated treatments, particularly inappropriate drugs, and are nonapplicable to non-drug treatments, surgery, or diagnostic tests. As a result, due to the insufficient data, the prevalence of LvC is somewhat underestimated. Additionally, due to the low prevalence of some LvC or HvC treatments, some of the presented results are not generalizable and have to be confirmed in future research that is based on larger sample sizes.

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SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-210439.

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Articel 2: Associations Between Low-Value Medication in Dementia and Healthcare Costs

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ORIGINAL RESEARCH ARTICLE

Associations Between Low-Value Medication in Dementia and Healthcare Costs

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Abstract

Background Low-value medications (Lvm) provide little or no benefit to patients, may be harmful, and waste healthcare resources and costs. Although evidence from the literature indicates that Lvm is highly prevalent in dementia, evidence about the financial consequences of Lvm in dementia is limited. This study analyzed the association between receiving Lvm and healthcare costs from a public payers' perspective.

Methods This analysis is based on data of 516 community-dwelling people living with dementia (PwD). Fourteen Lvm were extracted from dementia-specific guidelines, the German equivalent of the Choosing Wisely campaign, and the PRISCUS list. Healthcare utilization was retrospectively assessed via face-to-face interviews with caregivers and monetarized by standardized unit costs. Associations between Lvm and healthcare costs were analyzed using multiple linear regression models.

Results Every third patient ($n=159$, 31%) received Lvm. Low-value antiphlogistics, analgesics, anti-dementia drugs, sedatives and hypnotics, and antidepressants alone accounted for 77% of prescribed Lvm. PwD who received Lvm were significantly less cognitively impaired than those not receiving Lvm. Receiving Lvm was associated with higher medical care costs ($b=2959$ €; 95% CI 1136–4783; $p=0.001$), particularly due to higher hospitalization ($b=1911$ €; 95% CI 376–3443; $p=0.015$) and medication costs ($b=905$ €; 95% CI 454–1357; $p<0.001$).

Conclusion Lvm were prevalent, more likely occurring in the early stages of dementia, and cause financial harm for payers due to higher direct medical care costs. Further research is required to derive measures to prevent cost-driving Lvm in primary care, that is, implementing deprescribing interventions and moving health expenditures towards higher value resource use.

Key Points

Low-value medications are highly prevalent in dementia care and could lead to higher costs for public payers.

Low-value medications occur in the early stages of dementia (i.e., at the beginning of the disease).

Implementing deprescribing interventions could improve outcomes for patients while saving resources.

1 Introduction

Rapidly increasing healthcare expenditures are challenging health systems worldwide. Due to high healthcare costs, debates have risen about unnecessary expenditure and whether spending focus should move toward higher-value resource use [1]. Shrank et al. [2] estimated the total annual cost of waste to be between US$760 billion to US$935 billion in the US, representing 25% of the total US healthcare spending. Up to US$101.2 billion could be traced back to overtreatment and low-value care, defined as care unlikely to

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benefit patients regarding potential harms, costs, or available alternatives [2–4].

Low-value care or overtreatment are related terms classified under the overarching category of overuse [5]. Evidence to date has been derived primarily from administrative and routinely collected data and focused mainly on the prevalence of low-value medical tests and procedures. In contrast, prescribed low-value medications (Lvm) were underrepresented in recent research [6, 7]. Further, current publications emphasize evidence gaps in the factors promoting overuse (provider vs patient-centered) and for downstream harmful effects (physical, psychological, economic), especially financial harms [8, 9]. In addition, only 15% of low-value care recommendations report economic value at all, representing a significant evidence gap in decision support for physicians and other stakeholders in healthcare [10].

Chronic age-associated diseases such as dementia still represent one of the highest societal and economic burdens on healthcare systems in an aging population worldwide. While there are 57 million people living with dementia (PwD) worldwide, a recent forecast estimates this figure will reach 153 million in < 30 years [11]. Without a prospect of cure, dementia care aims to ensure the best possible individualized care. However, only 39% of people who screened positive for dementia received a formal diagnosis [12], only 30% of PwD are treated with adequate anti-dementia drugs [13, 14], and only 36% were provided with non-drug therapies following the pertinent guidelines [15].

Moreover, a preceding study revealed that at least 31% of the PwD received low-value care, particularly Lvm associated with reduced quality of life and increased hospitalization [16]. In addition, 93% of PwD were affected by at least one drug-related problem and associated additional costs, suggesting that Lvm could also amplify adverse downstream effects for both PwD and payers [17]. Previous studies show the likelihood for PwD and aged individuals receiving low-value prescriptions increases with age, degree of comorbidity, and higher deficits in their daily living [7, 18]. While medication costs in PwD likewise increase with comorbidity and functional impairment, severely cognitively impaired patients are more likely treated with less high-priced drugs, suggesting inadequate medication and poor resource use [19].

However, as long as financial resources are wasted on low-value care, they will not be available to address the unmet needs of current and future PwD, underlining the ethical, economic, and political challenges associated with low-value care [3]. Despite the projected prevalence of dementia and the associated economic and societal impacts, there is insufficient evidence to date on the harms and costs associated with low-value medications in dementia care. Therefore, the objective of this analysis was to analyze the association between receiving Lvm and direct medical care costs from a payers' perspective in community-dwelling PwD.

2 Materials and Methods

2.1 Design of the DelpHi-MV Trial, Setting, and Participant Flow

This cross-sectional analysis is based on baseline data of the cluster-randomized, controlled interventional trial DelpHi-MV (Dementia: life- and person-centered Help in Mecklenburg-Western Pomerania) [20]. Initially, 125 general practitioners (GPs) screened 6838 patients in their practices for dementia using the short interview-based DemTect screening procedure [21]. A total of 1166 (17%) patients met the eligibility criteria (DemTect < 9, aged ≥ 70 years, living at home), were informed about the study by their GP, and were asked to provide written informed consent as approved by the Ethical Committee of the Chamber of Physicians of Mecklenburg-Western Pomerania (registry number BB 20/11). Informed consent was provided by a total of 634 eligible patients (54%). The enrolment and thus the data collection at baseline began on 1 January 2012 and ended on 31 December 2014 [20, 22]. The baseline assessment was completed for 516 PwD, constituting the basis for the presenting analysis. The comprehensive design and participant flow have been described in more detail elsewhere [22].

2.2 Sociodemographic and Clinical Characteristics

Sociodemographic data (age, sex, living situation) and the following clinical variables covering the 12 preceding months were assessed at baseline through a comprehensive, standardized, computer-assisted interview carried out by dementia-specific qualified nurses: cognitive impairment according to the Mini-Mental State Examination (MMSE) [23], comorbidity according to the number of ICD-10 (International Statistical Classification of Diseases and Related Health Problems, 10th revision) diagnoses listed in the GP files [24], depression symptoms according to the Geriatric Depression Scale (GDS) [25], and deficits in daily living activities according to the Bayer Activities of Daily Living Scale (B-ADL) [26].

Furthermore, comorbidities were assessed using a score based on the Charlson comorbidity index (CCI) [27], which considered the following diseases: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, mild liver disease, diabetes without chronic complication, diabetes with chronic complication, hemiplegia or paraplegia, renal disease, any

malignancy, including lymphoma and leukemia, except malignant neoplasm of skin, moderate or severe liver disease, metastatic solid tumor, and AIDS/HIV [27].

2.3 Healthcare Resource Utilization

The utilization of healthcare resources was also assessed within the baseline interview [20]. The questionnaires captured detailed information about the frequencies of the utilization of the following medical care services: physician consultation (GP, specialists), medication, aids, other outpatient treatments (e.g., occupational, physical and speech therapy), and in-hospital care (acute and planned in-hospital treatment). Besides the number of hospital admissions, the days per stay were also recorded. To improve the validity and precision of the data, study nurses interviewed caregivers, participants, and professional care staff wherever possible.

2.4 Low-Value Medication Measurement

The following three sources were used as references to elicit Lvm in dementia: (i) the German "S3 Guideline: Dementia" published by the German Association for Psychiatry, Psychotherapy and Psychosomatics and the German Society for Neuroscience [28], which lists selected medications that are ineffective and should be avoided; (ii) the PRISCUS list [29], including a total of 83 substances from 18 drug classes that are potentially inadequate for elderly individuals; and (iii) defined harmful recommendations of the German counterpart of the international "Choosing Wisely" campaign [30]. Two reviewers and, in the case of deviations, a third reviewer selected the Lvm-related recommendations according to the following criteria: (i) relevance, (ii) targeted audience, (iii) differentiation criteria for inappropriateness, as well as (iv) evaluability in the data set used for the present analysis [31]. A total of 51 Lvm recommendations were identified. Due to overlap or duplication, recommendations were broken down into individual components and grouped into measurable treatments according to the suggestions of previous studies [6, 31]. In conclusion, 14 measurable active substance classes, including 40 active substances identified as Lvm treatments, provided the basis for this analysis. All Lvm used are demonstrated in Table 1, including active substances, data requirements, and counts. The comprehensive selection process of the respective treatments has been described in more detail elsewhere [32].

2.5 Cost Analysis

A bottom-up prevalence-based cost-of-illness design was used to calculate the average healthcare costs per person living with dementia for a retrospective period of 12 months [33]. In this analysis, healthcare costs comprise the direct costs for medical care services from the payers' perspective. Average medical care costs per patient were calculated using the captured healthcare resource utilization added by their respective published standardized unit costs [34]. When current unit costs were not available, they were extrapolated to 2020 using the average annual inflation rate (for 2016: 0.5%, 2017: 1.5%, 2018: 1.8%, 2019: 1.5%, 2020: 0.5%) [35]. Costs were calculated in Euros (€). Formal and informal care and indirect costs, such as lost productivity, were not considered in this analysis. Detailed information on the monetary valuation of the respective services is summarized in Table 2.

2.6 Statistical Analysis

Study participants' sociodemographic and clinical characteristics, health resource utilization, and healthcare costs were presented using descriptive statistics. The statistical significance of group differences (receiving no Lvm vs at least one Lvm) was determined using t tests and Fisher exact tests. Multiple linear regression models were performed to assess the associations between Lvm and healthcare costs. The dependent variables were total medical care costs from the payers' perspective and the following subcategories: costs for physician treatments (GP and specialists), inpatient treatments, medications, medical aids, and outpatient treatments, resulting in a total of six different models. Lvm (dichotomous: receiving no Lvm vs at least one Lvm) was used as an independent variable. Models were furthermore adjusted for the following sociodemographic and clinical factors: age, sex, cognition (MMSE), functional impairment (B-ADL), depression (GDS), as well as patients' diagnoses (dichotomous: yes/no for each) according to the CCI and number of diagnoses (number of ICD-10 diagnoses) to consider the context in which treatments were prescribed and to minimize confounding. Since patients were recruited in different clusters (i.e., GP practices), patient outcomes, treatment, and care could be stochastically dependent on the GP practice. Therefore, we used random effects to adjust for the effects of the clusters in each of our regression models. Due to the highly skewed distribution of medical care costs, standard errors and confidence intervals were determined using nonparametric bootstrapping (2000 replications) [36]. All statistical analyses were performed in STATA/IC 16 [37].

Table 1 14 Low-value medication (Lvm) treatments: active substances included, data requirements, and counts

Lvm by active substance class	Active substance (further condition)	Data requirements[a]	PwD receiving Lvm, *n* (%)
Low-value antiphlogistics/analgesics	Dexketoprofen	ATC (M01AE17)	59 (30.41)
	Etoricoxib	ATC (M01AH05)	
	Indometacin	ATC (M02AA23, M01AB01)	
	Meloxicam	ATC (M01AC06)	
	Naproxen	ATC (M01AE02)	
	Diclofenac	ATC (M01AB05, M02AA15)	
Low-value antidementia drug treatments	Memantine (does not comply with the guidelines for mild dementia)	ATC (N06DX01) MMSE (≥20)	37 (19.07)
	Naftidrofuryl	ATC (C04AX21)	
	Piracetam	ATC (N06BX03)	
	Dihydroergotoxine	ATC (N06DX07)	
Low-value sedatives/hypnotics	Chloral hydrate	ATC (N05CC01)	28 (14.43)
	Chlordiazepoxide	ATC (N05BA02)	
	Clobazam	ATC (N05BA09)	
	Diazepam	ATC (N05BA01)	
	Zopiclone	ATC (N05CF01)	
	Diphenhydramine	ATC (N05CM20)	
	Doxylamine	ATC (N05CM21)	
	Medazepam	ATC (N05BA03)	
	Nitrazepam	ATC (N05CD02)	
	Zolpidem	ATC (N05CF02)	
Low-value antidepressants	Amitriptyline	ATC (N06AA09)	25 (12.89)
	Amitriptyline oxide	ATC (N06AA25)	
	Doxepin	ATC (N06AA12)	
	Trimipramine	ATC (N06AA06)	
Low-value antihypertensives	Clonidine	ATC (S01EA04, C02AC01)	16 (8.25)
	Doxazosin	ATC (C02CA04)	
	Methyldopa	ATC (C02AB01)	
Low-value spasmolytics	Solifenacin	ATC (G04BD08)	10 (5.15)
	Tolterodine	ATC (G04BD07)	
Low-value antipsychotics	Levomepromazine	ATC (N05AA02)	7 (3.6)
	Olanzapine	ATC (N05AH03)	
	Haloperidol	ATC (N05AD01)	
	Quetiapine (does not comply with the guidelines for agitation and aggression)	ATC (N05AH04) NPI[b] (≥1)	
Low-value antiarrhythmics	Acetyldigoxin	ATC (C01AA02)	4 (2.06)
	Flecainide	ATC (C01BC04)	
	Sotalol	ATC (C07AA07)	
Low-value muscle relaxants	Baclofen	ATC (M03BX01)	4 (2.06)
	Tetrazepam	ATC (M03BX07)	
Low-value antiemetics	Dimenhydrinate	ATC (A04AB02)	2 (1.03)
Low-value ergotamine	Dihydroergocryptine	ATC (N04BC03)	1 (0.52)
Low-value vitamin E		ATC (A11HA03)	1 (0.52)

ATC Anatomical Therapeutic Chemical, *Lvm* low-value medications, *MMSE* Mini-Mental State Examination, range 0–30, higher score indicates better cognitive function, *NPI* Neuropsychiatric Inventory, score ≥ 5 indicates clinically relevant symptoms, *PwD* people with dementia

[a]Beyond demographic data (e.g., age)

[b]Score for agitation and aggression

Table 2 Methods and used unit costs for monetary valuation of medical care services (based on Michalowsky et al. [53])

Cost categories	Services	Units	Unit costs[a]	Unit cost and source for monetary valuation
Outpatient physician treatment	GP or specialists	Visits	21.16 €–82.38 €, depending on specialization	Cost per visit [34]
Inpatient treatment	In-hospital treatment and rehabilitation	Days	598.97 € and 123.07 €, respectively	Average per diem cost for in-hospital treatment in Mecklenburg-Western Pomerania and for specialization of rehabilitation [34]
Medications	Regularly prescribed drugs (Rx-drugs)	Quantity	Market prices, 256.12 €[b]	Pharmaceutical Index of the Scientific Institute of the AOK [54]
Medical aids	Aids such as tub-lifts, tub-seats, walking sticks, walkers, and others	Quantity	Market prices, 170.61 €[b]	Market prices [34]
Other outpatient treatment	Occupational therapy, speech therapy, physiotherapy, and others	Visits	27.62 €	Cost per contact and reimbursement schedules of statutory health insurance [55]

AOK Allgemeine Ortskrankenkasse, *GP* general practitioner

[a]Inflation included

[b]When drugs, aids or services were unknown, or market prices were not available

3 Results

3.1 Sociodemographic and Clinical Characteristics

Study participants were primarily female (60%), on average 80 (SD 5.5) years old, and mildly cognitively (MMSE mean score 22.2, SD 5.4) and functionally impaired (B-ADL mean score 3.7, SD 2.6). PwD who received Lvm ($n=159$) were slightly younger (79 vs 80 y, $p=0.073$), were less cognitively impaired (23.0 vs 21.7, $p=0.013$), took on average more drugs (9 vs 7, $p<0.001$), and were more depressed (3.5 vs 3.0, $p=0.032$), according to the GDS, compared with PwD who received no Lvm treatments ($n=357$). There were no significant differences for any of the other variables. The sample characteristics are presented in Table 3.

3.2 Healthcare Resource Utilization and Costs

PwD who received at least one Lvm had higher utilization of medical treatments. Significant differences were observed in the prevalence (32 vs 23%, $p=0.045$) and frequency (1.2 vs 0.6, $p=0.037$) of specialist consultations. Moreover, PwD with Lvm had more inpatient treatments (39 vs 26%, $p=0.007$), especially acute (28 vs 19%, $p=0.019$) and planned (14 vs 7%, $p=0.019$) in-hospital treatments, and they stayed longer in hospitals (6 vs 3 days, $p=0.009$) than PwD without Lvm. They also received significantly more anti-dementia drugs (37 vs 26%, $p=0.020$) and used other outpatient treatments more often (68 vs 59%, $p=0.039$). All results on the percentage and frequency of healthcare resource utilization are depicted in Table 4.

Total cost for medication was valued at 181,153 € for the total sample, of which Lvm accounts for 29,983 € (17%) and the remaining medications for 151,170 € (83%). Payers' expenditures for PwD receiving Lvm were significantly higher than those for PwD who did not receive any Lvm (8514 € vs 5539 €, $p<0.001$). This trend was also evident for specialists' costs (382 € vs 305 €, $p=0.035$), cost for inpatient treatments (4501 € vs 2380 €, $p=0.003$), in particular, cost for acute in-hospital treatments (2996 € vs 1749 €, $p=0.031$), and also medication costs (2450 € vs 1538 €, $p<0.001$). Cost differences between Lvm recipients and Lvm non-recipients are presented in Table 5.

3.3 Association Between Low-Value Medication Treatment and Healthcare Costs

PwD who received Lvm had significantly higher medical treatment costs ($b=2959$ €; 95% CI 1136–4783; $p=0.001$) due to significantly higher costs for inpatient treatments ($b=1911$ €; 95% CI 376–3443; $p=0.015$) and medications ($b=905$ €; 95% CI 454–1357; $p<0.001$). In contrast, there were no significant associations between receiving Lvm and costs for outpatient physician treatments, medical aids, and other outpatient treatments. The latter model was no longer significant.

Regarding sociodemographic and clinical co-variables, age was associated with less direct medical care costs. In contrast, functional and cognitive impairment was

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Table 3 Sociodemographic and clinical characteristics of the total sample and subsample

Characteristic	Total sample $n=516$	PwD receiving Lvm		p value[a]
		Yes $n=159$	No $n=357$	
Age, years				
Mean (SD)	80.0 (5.5)	79.3 (5.5)	80.3 (5.5)	0.073[b]
Range	70–100	70–96	70–100	
Sex, *n* (%)				
Female	307 (59.5)	104 (65.4)	203 (56.9)	0.080[c]
MMSE				
Mean (SD)	22.2 (5.4)	23.0 (4.4)	21.7 (5.7)	**0.013**[b]
Range	3–30	8–30	3–30	
Severity of dementia, *n* (%)				
No hint for dementia, MMSE score > 26	108 (22.7)	33 (21.0)	75 (23.5)	
Mild dementia, MMSE score 20–26	239 (50.2)	94 (59.9)	145 (45.5)	
Moderate dementia, MMSE score 10–19	107 (22.5)	27 (17.2)	80 (25.1)	
Severe dementia, MMSE score < 10	22 (4.6)	3 (1.9)	19 (6.0)	
Living situation, *n* (%)				
Alone	260 (50.9)	84 (52.8)	176 (50.0)	0.568[c]
Number of ICD-10 diagnoses				
Mean (SD)	13.2 (7.8)	13.7 (7.3)	12.9 (8.0)	0.318[b]
Range	1–58	3–36	1–58	
Formally diagnosed with dementia, *n* (%)				
Yes	366 (71.1)	110 (69.6)	256 (71.7)	0.674[c]
Charlson Score				
Mean (SD)	3.3 (2.3)	3.3 (2.1)	3.4 (2.3)	0.632[b]
Range	0–15	0–15	0–13	
Number of drugs taken				
Mean (SD)	7.3 (3.6)	8.8 (4.1)	6.7 (3.1)	**< 0.001**[b]
Range	0–26	1–26	0–18	
B-ADL				
Mean (SD)	3.7 (2.6)	3.5 (2.3)	3.7 (2.7)	0.357[b]
Range	1–10	1–10	1–10	
GDS				
Mean (SD)	3.2 (2.5)	3.5 (2.8)	3.0 (2.3)	**0.032**[b]
Range	0–14	0–14	0–13	

Values in bold indicate $p < 0.05$

B-ADL Bayer–Activities of Daily Living Scale, range 0–10, lower score indicates better performance, *GDS* Geriatric Depression Scale, sum score 0–15, score ≥ 6 indicates depression, *ICD* International Statistical Classification of Diseases and Related Health Problems, *Lvm* low-value medications, *MMSE* Mini-Mental State Examination, range 0–30, higher score indicates better cognitive function, *PwD* people with dementia, *SD* standard deviation

[a]Referring to PwD who received no Lvm vs. at least one Lvm

[b]Differences in means: *t* test two-tailed

[c]Differences in proportions: Fisher's exact tests

associated with higher medical care costs. Additionally, comorbidities such as chronic pulmonary, rheumatic disease and moderate or severe liver disease and diabetes with chronic complications were also associated with increased medical treatment costs. Table 6 summarizes the associations between healthcare costs and Lvm treatments.

Table 4 Percentage and frequency of healthcare resource utilization

Medical treatments	Total sample $n=516$	PwD receiving Lvm		p value[a]
		Yes $n=159$	No $n=357$	
Percentage of utilization, n (%)				
Outpatient physician treatment	516 (100.0)	159 (100.0)	357 (100.0)	
GP	516 (100.0)	159 (100.0)	357 (100.0)	
Specialists	128 (25.5)	48 (31.6)	80 (22.8)	**0.045**[b]
Inpatient treatment	153 (30.2)	61 (38.6)	92 (26.4)	**0.007**[b]
Acute in-hospital treatment	109 (21.8)	44 (28.4)	65 (18.8)	**0.019**[b]
Planned in-hospital treatment	47 (9.4)	22 (14.3)	25 (7.2)	**0.019**[b]
Rehabilitation	31 (6.1)	12 (7.6)	19 (5.5)	0.424[b]
Medications	484 (98.4)	158 (99.4)	326 (97.9)	0.447[b]
Anti-dementia drugs	144 (29.5)	58 (36.5)	86 (26.1)	**0.020**[b]
Medical aids	499 (98.6)	151 (97.4)	348 (99.2)	0.209[b]
Other outpatient treatment	315 (61.6)	108 (68.4)	207 (58.6)	**0.039**[b]
Frequency of utilization, mean (SD)				
Number of GP contacts	7.00 (6.4)	6.9 (5.3)	7.1 (6.8)	0.745[c]
Number of specialist contacts	0.8 (2.9)	1.2 (4.5)	0.6 (1.6)	**0.037**[c]
Days stayed in-hospital per year	4.0 (9.6)	5.7 (11.2)	3.3 (8.6)	**0.009**[c]
Number of medical aids	4.7 (2.7)	5.0 (2.8)	4.6 (2.7)	0.138[c]
Number of other outpatient treatment visits	11.2 (35.7)	10.8 (17.0)	11.3 (41.4)	0.881[c]

Values in bold indicate $p < 0.05$

GP General practitioner, *Lvm* low-value medications, *PwD* people living with dementia *SD* standard deviation

[a]Referring to PwD who received no Lvm vs at least one Lvm

[b]Differences in proportions: Fisher's exact tests

[c]Differences in means: *t* test two-tailed

Table 5 Healthcare costs [€] among people living with dementia treated with low-value medications

Item	Total sample $n = 516$ Mean (SD)	PwD receiving Lvm		p Value[a]
		Yes, $n = 159$ Mean (SD)	No, $n = 357$ Mean (SD)	
Medical treatments	6501 (7899)	8514 (9260)	5539 (6973)	**< 0.001**[b]
Outpatient physician treatment	499 (424)	549 (472)	477 (400)	0.074[b]
GP	170 (155)	167 (128)	171 (165)	0.745[b]
Specialists	329 (384)	382 (451)	305 (347)	**0.035**[b]
Inpatient treatment	2994 (6883)	4501 (8349)	2380 (6018)	**0.003**[b]
Acute in-hospital treatment	2136 (5952)	2996 (6875)	1749 (5455)	**0.031**[b]
Planned in-hospital treatment	759 (3492)	1101 (4049)	607 (3209)	0.144[b]
Rehabilitation	175 (769)	254 (918)	140 (690)	0.128[b]
Medications	1833 (1919)	2450 (2372)	1538 (1581)	**<0.001**[b]
Medical aids	933 (1071)	933 (984)	932 (1108)	0.992[b]
Other outpatient treatment	130 (772)	120 (509)	134 (864)	0.844[b]

Values in bold indicate $p < 0.05$

GP General practitioner, *Lvm* low-value medications, PwD people with dementia, *SD* standard deviation

[a]Referring to PwD who received no Lvm vs at least one Lvm

[b]Differences in proportions: Fisher's exact tests

[c]Differences in means: *t* test two-tailed

Table 6 Multivariable associations between PwD who received Lvm and direct medical care costs

	Medical care costs	Outpatient physician treatment	Inpatient treatment	Medications	Medical aids	Other outpatient treatment
PwD who received Lvm *b* (SE) [95% CI]	2959 (930)** [1136–4783]	63 (46) [−27 to 153]	1911 (782)* [376–3443]	905 (231)*** [454–1357]	−10 (99) [−205 to 183]	31 (44) [−56 to 118]
R^2 overall	0.22***	0.08***	0.16***	0.18***	0.16***	0.10‡
N	427	449	436	448	444	449

Linear mixed models with random effects for general practitioner

The models used were adjusted for sociodemographic and clinical variables: age, sex, cognition (MMSE), functional impairment (B-ADL), depression (GDS), and comorbidities (CCI)

b observed coefficient, *B-ADL* Bayer–Activities of Daily Living Scale, *CCI* Charlson comorbidity index, *CI* confidence interval, *GDS* Geriatric Depression Scale, *Lvm* low-value medications, *MMSE* Mini-Mental State Examination, *PwD* people with dementia, *SE* standard error

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

‡*p*-value not significant

4 Discussion

Derived from patterns of healthcare resource utilization by community-dwelling PwD, this analysis adds evidence about promoting factors and the downstream financial consequences of low-value dementia medical care, demonstrating that Lvm represents a noticeable part of total medication costs (17%) associated with increased healthcare costs from the public payers' perspective. Higher medical treatment costs underline this finding, primarily due to higher inpatient treatment and medication costs. Additionally, PwD receiving Lvm were more frequently treated by physician specialists and outpatient therapies, more often hospitalized, and took a higher number of drugs, particularly anti-dementia drugs. In addition, the results revealed that younger and, to all appearances, early-stage and thus healthier PwD are more likely to receive Lvm.

Assuming healthcare costs would increase because of Lvm, it is uncertain whether this is due to individual patient-related or systemic provider-centric factors. Several studies have already examined the patient-related factors that increase the likelihood of receiving Lvm, reporting higher age, degree of comorbidity, and higher deficits in activities of daily living [7, 18]. The findings of our descriptive analysis of primary data are not in line with these results. Our sample showed no significant differences in age, comorbidity, or functional impairment between PwD with and without Lvm.

In contrast, those who received Lvm were significantly less cognitively impaired but more depressive than PwD not receiving Lvm treatments. While an elevated depression score is potentially suggestive of mental comorbidities, better cognitive function indicates healthier patients. However, Michalowsky et al. [19] demonstrated that increasing cognitive impairment is associated with fewer drugs, meaning that PwD who are less cognitively impaired receive more medication. Our results show that PwD receiving Lvm took more drugs (9 vs 7) than PwD without Lvm treatments. A higher number of drugs could promote drug-related problems that could cause harm to both the patient and the healthcare system, for example due to increasing hospitalization [38, 39]. Based on our findings, especially in the early stages of dementia, there is a risk for Lvm, which clinicians should consider as early as possible on the patient journey.

Regarding the increasing inpatient treatment costs, Wohlgemuth et al. [17] revealed an association between higher inpatient costs and inappropriate drug choice, which is significantly linked to Lvm treatments. Also, a recent analysis showed an increased likelihood of hospitalization for PwD who received Lvm, underscoring this tendency [32]. These findings are consistent with the present study, demonstrating the higher use of acute (28 vs 19%) and planned (14 vs 7%) in-hospital treatments in PwD receiving Lvm compared with PwD without Lvm treatments.

Recently published studies examined the downstream effects of low-value care procedures in hospitals. They revealed that patients who received low-value care were associated with higher Medicare costs and longer lengths of stay [40, 41], which is in line with the results of our analysis, demonstrating that PwD who received Lvm treatments were more frequently hospitalized (39 vs 26%) and stayed longer in hospitals (6 vs 3 days). The higher utilization of in-hospital services resulted in higher inpatient treatment costs (4501 € vs 2380 €) compared with PwD without Lvm treatments. Hospitalization is a crucial cost-driver and is connected to Lvm in dementia. Further research is needed to generate evidence about the causality between both factors

and identify strategies to avoid cost-intensive unnecessary hospitalizations.

According to outpatient physician treatments, specialists have a crucial role in dementia care since they increasingly provide differential diagnostic and post-diagnostic support by prescribing anti-dementia drug treatment [42]. The present analysis shows that the consultation prevalence of specialists (32 vs 23%) and prescription prevalence of anti-dementia drugs (37 vs 26%) were higher for PwD receiving Lvm than for PwD without Lvm treatments. Despite their crucial role regarding post-diagnostic dementia care, outpatient physicians could likewise promote Lvm. A previous survey of GPs showed that although 57% of the GPs have seen negative consequences, 67% regularly provided low-value care because they want to offer interventions instead of watchful waiting to meet their patients' expectations [43]. Further studies reported cognitive biases, comprising an overestimation of benefits and an underestimation of harms from both patient and physician perspectives [44–46]. In principle, physicians should base their decisions for or against treatment on the available evidence. Still, while the focus is on efficacy and effectiveness, according to Korenstein et al. [8], more research is needed to expand the evidence base about harms from treatments. For Lvm, this extends beyond patient-centered outcomes to financial or economic harms on the system level [10].

This analysis shows that Lvm in dementia care is widespread, occurs across sectors and providers, and is associated with higher costs. However, cross-sectional data alone cannot represent cause and effects. Longitudinal analyses are needed to confirm the findings and to include other outcomes, such as the effect on institutionalization, to examine group differences in nursing home admissions among community-dwelling PwD with and without Lvm. In addition to the costs and utilization of health resources, further research should consider the long- and short-term physical and psychological consequences and expand the evidence on (cost) effectiveness.

As diverse as the stakeholders and drivers of low-value dementia care are, solutions must be equally varied, such as implementing deprescribing interventions [47]. Therefore, multiple levers must be pulled to foster high-value care and treatments [3]. In times of increasing numbers of PwD and the associated growing socioeconomic burden on healthcare systems worldwide, more intersectoral research on low-value care is required to generate evidence about the causal effect of Lvm on patient-reported and health economic outcomes. Also, separate modularized solutions or interventions should be developed to prevent low-value care in outpatient and inpatient settings. Further research should provide quantitative evidence of the harm from low-value care to healthcare stakeholders to broaden the rational basis for decision making, especially for healthcare payers.

4.1 Limitations

This study used baseline data from the DelpHi-MV trial [20], resulting in limited generalizability. First, the data and related findings refer to a rural region in North-Eastern Germany and cannot simply be transferred to urban settings and the West or South. Nevertheless, due to the large primary care sample with GPs in a leading role, our findings are representative of other regions with community-dwelling PwD. Furthermore, primary data and utilization data were collected directly from the patients; other data sources, such as health insurers, were not accessible. However, we performed a standardized data assessment and obtained valid information on relevant clinical dimensions not usually available in secondary data analyses. The completeness and accuracy of information may be affected by the limited cognitive capacities of the participating PwD. Considering the clinical course of dementia disease, most study participants had mild cognitive impairments or early-stage dementia. However, to increase the validity of our data, we obtained additional information from care providers and caregivers in proxy interviews. In addition, the participating PwD were on average 80 years old and were community-dwelling. Therefore, findings cannot simply be transferred to PwD residing in institutions.

Clinical evidence-based guidelines and consensus-based expert publications were used to define low-value interventions, which leads to additional limitations. First, the present analysis does not cover all Lvm. Therefore, the demonstrated prevalence of Lvm is somewhat underestimated. The classification as low-value care also depends on the perspective. In the present analysis, the sources represent an expert perspective rather than the patient perspective regarding unwanted care. In addition, the respective recommendations overemphasize the clinical rationale while not reflecting the economic evidence [10]. A broader evidence base for Lvm must be included from the outset to implement effective strategies minimizing Lvm.

In addition, the results may be limited due to the use of the PRISCUS list [29]. In recent years, other evidence-based lists such as the FORTA [48] or EU(7)-PIM [49] lists, which are more contemporary, have been developed and published. However, the design of the DelpHi-MV trial [20] was developed earlier and targeted drug data collection according to the PRISCUS list [29], which remains a common tool in health services research to indicate potentially inappropriate drugs. However, demonstrated results might change if different lists are used. Further research is therefore needed to detect differences in Lvm and costs according to the other available Lvm lists.

Furthermore, although the PRISCUS list [29] is an explicit tool that offers practical advantages for large-scale epidemiologic studies by directly collecting or measuring

relevant data, it neglects clinical contextual factors and circumstances and individual patient needs [50, 51]. As a result, prescriptions may have been recorded as Lvm even though the treatment provided was appropriate, representing a conflict of goals already described by Schwartz et al. [52]. These clinical contextual factors were unknown in this analysis. Therefore, further research is needed to clarify on an individual patient level if Lvm represents an inappropriate medical treatment with an existing better alternative and if the association between Lvm, patient-reported outcomes, and costs remain significant.

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Articel 3: Impact of low-value medications on quality of life, hospitalization and costs - A longitudinal analysis of patients living with dementia

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RESEARCH ARTICLE

Impact of low-value medications on quality of life, hospitalization and costs – A longitudinal analysis of patients living with dementia

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Abstract

Introduction: This study aimed to analyze the impact of low-value medications (Lvm), that is, medications unlikely to benefit patients but to cause harm, on patient-centered outcomes over 24 months.

Methods: This longitudinal analysis was based on baseline, 12 and 24 months follow-up data of 352 patients with dementia. The impact of Lvm on health-related quality of life (HRQoL), hospitalizations, and health care costs were assessed using multiple panel-specific regression models.

Results: Over 24 months, 182 patients (52%) received Lvm at least once and 56 (16%) continuously. Lvm significantly increased the risk of hospitalization by 49% (odds ratio, confidence interval [CI] 95% 1.06–2.09; $p = 0.022$), increased health care costs by €6810 (CI 95% −707€–14,27€; $p = 0.076$), and reduced patients' HRQoL ($b = -1.55$; CI 95% −2.76 to −0.35; $p = 0.011$).

Discussion: More than every second patient received Lvm, negatively impacting patient-reported HRQoL, hospitalizations, and costs. Innovative approaches are needed to encourage prescribers to avoid and replace Lvm in dementia care.

KEYWORDS
Alzheimer's disease, dementia, health care costs, health care resources, health-related quality of life, hospitalization, low-value care

Highlights

- Over 24 months, more than every second patient received low-value medications (Lvm).
- Lvm negatively impact physical, psychological, and financial outcomes.
- Appropriate measures are needed to change prescription behaviors.

RESEARCH IN CONTEXT

1. **Systematic Review**: The authors reviewed the literature using PubMed. Although low-value medications (Lvm) in dementia care, that is, medications unlikely to benefit patients but to cause harm, are associated with negative physical, psychological, and financial outcomes, longitudinal effects on patient-relevant outcomes have rarely been reported.
2. **Interpretation**: This longitudinal analysis revealed a negative impact of Lvm on patient-reported health-related quality of life, hospitalizations, and direct health care costs.
3. **Future Directions**: Appropriate and effective approaches are required to encourage prescribers to avoid Lvm in dementia care wherever possible. Furthermore, adequate alternative treatments are needed as early as possible in the patient journey through the health care system to avoid downstream effects for patients and resource-burdening for health systems.

1 | BACKGROUND

Overtreatment and low-value care, such as potentially inappropriate medications or unnecessary tests and procedures, are unlikely to benefit patients, cause harm, waste scarce health care resources, and increase costs.[1–3] While approaches such as inappropriate drug use, medication interactions or polypharmacy reflect especially the medical perspective on patient safety, low-value care covers a broader perspective that includes ineffective, inefficient or unwanted treatment and care.[4] Low-value care represents approximately US$101.2 billion annually, contributing to 25% of wasteful health care expenditures in the US.[3,5] Despite the ever-expanding evidence underscored by an increased number of guidelines and recommendations against medical overuse through initiatives such as Choosing Wisely or listing of potentially inappropriate medications, the percentage of patients receiving low-value care and spending has not declined significantly in recent years.[6]

Therefore, Korenstein et al.[7] pleaded for comprehensive reporting of the negative effects of medical overuse, including physical, psychological, financial and social effects and consideration of treatment burden. Claims data have been a major source of evidence on trends in the prevalence of low-value tests and procedures.[8] However, claims data cannot provide information about certain relevant patient-centered outcomes. Consequently, the prescription and utilization of low-value medications (Lvm), that is, medications for which the risk of harm exceeds the potential benefit and their downstream effects on patient-reported outcomes, such as health-related quality of life (HRQoL) and hospitalizations, have been underrepresented in recent research.[9–11]

Low-value care is highly prevalent in chronic age-associated diseases, such as dementia. Most patients living with dementia (PwD) have several coexisting diseases (multimorbidities) and receive several medications (polypharmacy).[12–14] Drug-related problems have been found in 93% of PwD associated with increased health care costs.[15–17] According to a recent forecast, the number of PwD will increase from 57 million to 153 million globally in less than 30 years.[18] The costs of dementia were estimated to exceed US$1 trillion worldwide in 2018 and could double by the end of this decade.[19] An approach to reducing Lvm promises to free resources to improve individualized health care for PwD while saving costs.

Previous cross-sectional studies have already revealed that receiving Lvm in dementia was associated with lower HRQoL and an increased risk for hospitalization and greater health care expenditures.[15,16,20,21] However, the longitudinal effects of Lvm on patient-relevant outcomes have been rarely reported. Therefore, the objective of the present analysis was to examine the effects of receiving Lvm on HRQoL, hospitalization and health care expenditures for PwD over 24 months.

2 | METHODS

2.1 | Data and study sample

This longitudinal analysis was based on data from the DelpHi-MV trial (Dementia: life- and person-centered Help in Mecklenburg-Western Pomerania).[22] Initially, 6838 patients were screened by 125 general practitioners (GP) for dementia using the DemTect procedure.[23] A total of 1166 patients (17%) met the eligibility criteria (DemTect < 9, ≥70 years old, living at home) and were subsequently informed about the study. Of these patients, 634 (54%) provided informed consent (approved by the Ethical Committee of the Chamber of Physicians of Mecklenburg-Western Pomerania – registry number: BB 20/11).

Comprehensive data assessments at baseline and after 12 and 24 months were completed by 352 PwD. The detailed participant flow is displayed in Figure S1. Patients who dropped out of the study had a significantly higher functional impairment (odds ratio [OR] 1.10; 95% confidence interval [CI], 1.01–1.19). The drop-out analysis is shown in Table S1. Additional analyses examining the drop-out reason by death revealed no significant differences in the distribution of mortality between those with and without Lvm and no effect of Lvm on drop-out by death (see Tables S2, S3, and Figure S2).The enrollment and data collection at baseline began on January 1, 2012, and ended on December 31, 2014. The detailed design has been described elsewhere.[24]

2.2 | Sociodemographic and clinical characteristics

Sociodemographic data (age, sex, living situation) and the following clinical variables were assessed through a comprehensive,

standardized, computer-assisted interview conducted by dementia-specific qualified nurses at baseline and 12 and 24 months after baseline in the participants' homes; cognitive impairment according to the Mini-Mental State Examination (MMSE)[25]; deficits in daily living activities according to the Bayer Activities of Daily Living Scale (B-ADL)[26]; depression symptoms according to the Geriatric Depression Scale (GDS)[27]; and comorbidities according to the number of ICD-10 (International Statistical Classification of Diseases and Related Health Problems, 10th revision) diagnoses listed in the GP files, complemented by the Charlson Comorbidity Index (CCI).[28,29]

2.3 | Lvm measurement

Medication data were captured within a standardized home medication review to assess all regularly taken drugs, including over-the-counter and prescribed medications, providing a more comprehensive picture of patients' Lvm use beyond documented prescriptions from physicians.[22,30,31] The medications recorded were validated with medication lists provided by the treating GP or, if available, by the administering nursing service. The following three sources were used as references for elaborating Lvm in dementia: (1) the German "S3 guideline: Dementia" published by the German Association for Psychiatry, Psychotherapy and Psychosomatics and the German Society for Neurology,[32] which lists selected medications that are ineffective and should be avoided, (2) the PRISCUS list,[33] including a total of 83 substances of 18 drug classes that are potentially inappropriate for elderly individuals; and (3) recommendations for avoiding harmful treatments of the German counterpart of the international "Choosing Wisely" campaign.[34] Three reviewers selected the Lvm-related recommendations according to the following criteria: (1) relevance; (2) targeted audience; (3) differentiation criteria for inappropriateness; and (4) evaluability in the dataset used for the present analysis. Thirty-nine active substances were identified and assigned to 10 measurable Lvm treatments. The selection process has been described in more detail elsewhere.[15,16]

Lvm variables were categorized as follows: (1) dichotomously (receiving Lvm vs. not receiving Lvm within 24 months); and (2) as a time referencing variable, considering the intensity of Lvm intake as a cumulative effect: (i) receiving Lvm at only one out of the three data assessments ("sporadic"); (ii) over 1 year – from baseline to 12-month follow-up or from 12 to 24 months of follow-up; or (iii) continuously over 2 years – from baseline to 24 months of follow-up. Table 1 demonstrates all Lvm used within this analysis.

2.4 | Patient-relevant outcomes

HRQoL was assessed using the 12-Item Short-Form Health Survey (SF-12), a short form of the SF-36,[35] measuring both physical dimensions (SF-12-PCS), including the perception of general health; physical functioning, bodily pain, and role limitations due to the physical health state; and mental dimensions (SF-12-MSC), comprising social functioning, mental health, vitality, and role limitations due to the emotional state.

Health care resource utilization was assessed using caregivers' and care professionals' proxy ratings to improve data validity and precision, providing detailed information about the frequency (number of visits, days stayed or quantities) of medical service utilization: physician consultations (GP, specialists), medication, aids, therapies (e.g., occupational, physical and speech therapy), and in-hospital care (acute and planned hospital admissions).[22] Additionally, hospitalizations were assessed dichotomously (at least one vs. none). Health care costs were calculated from the payers' perspective using standardized unit costs (inflated to 2022 and calculated in euros [€]).[36] Deltas were calculated (cost difference between baseline and 1 or 2 year(s) after baseline) to assess the change in total health care costs. Table S4 summarizes detailed information about the monetary valuation of the services.

2.5 | Statistical analysis

Data analyses included patients with complete baseline data. Missing follow-up values were imputed using multiple imputations by chained equations separately by randomization treatment allocation (intervention and control group).

Multivariable panel data regression models with specifications corresponding to the scale level of the respective outcome variable were fitted to assess the effects of Lvm on patients' HRQoL (linear regression), hospitalizations (logistic regression), and costs (linear regression). Lvm (independent variable) were operationalized as described above dichotomously (receiving Lvm vs. not receiving Lvm within 24 months) and as a time referencing variable (never, once and over periods of 1 or 2 years). The dependent variables were HRQoL (SF-12-MCS, SF-12-PCS), hospitalization (dichotomous: yes/no), and the delta of direct health care costs and the following cost categories: costs for physician treatments (GP and specialists), hospitalization, medications, medical aids, and therapies (e.g., occupational, physical, and speech therapy). All models were adjusted for sociodemographic (age, sex, living situation) and clinical factors (functional impairment (B-ADL), dementia diagnosis (ICD-10: F00, F01, F02, F03, G30), depression (GDS),coexisting morbidities (yes/no) according to the CCI, multimorbidity (number of ICD-10 diagnoses), and polypharmacy (i.e., $\geq$ 5 medications, yes/no) as well as the number of potential drug interactions according to the Risk-Check tool CAVE of the ABDA-Database) to consider the context in which Lvm were prescribed and to minimize confounding. Baseline outcome values were also included as a covariate to reduce residual variance and to account for interindividual variance. A lagged Lvm variable was added for models including the cumulative effect, considering whether Lvm had also been present in the previous period. Random effects were used to adjust for individuals regarding the panel-specific structure for HRQoL and hospitalizations and for GP practices concerning the delta of health care costs. Due to the highly skewed distribution of cost data, standard errors and confidence intervals were determined using nonparametric bootstrapping (2000 replications).[37]

TABLE 1 10 Low-value medication treatments: Active substances included, data requirements, and counts.

			PwD receiving LVM		
Lvm by active substance class[a]	Active substance (further condition)	Data requierements[b]	At baseline $n = 126$, n (%)	After 12 months $n = 120$, n (%)	After 24 months $n = 102$, n (%)
Low-value antiphlogistics/ analgesics	Dexketoprofen	ATC (M01AE17)	43 (34.1)	41 (34.2)	32 (31.4)
	Etoricoxib	ATC (M01AH05)			
	Indometacin	ATC (M02AA23, M01AB01)			
	Meloxicam	ATC (M01AC06)			
	Naproxen	ATC (M01AE02)			
	Diclofenac	ATC (M01AB05, M02AA15)			
Low-value antidementia drug treatments	Memantine (does not complies with the guidelines for mild dementia)	ATC (N06DX01) MMSE (≥20)	32 (25.3)	37 (30.8)	6 (5.9)
	Naftidrofuryl	ATC (C04AX21)			
	Piracetam	ATC (N06BX03)			
	Dihydroergotoxine	ATC (N06DX07)			
Low-value sedatives/ hypnotics	Chloral hydrate	ATC (N05CC01)	22 (17.5)	22 (18.3)	18 (17.6)
	Chlordiazepoxide	ATC (N05BA02)			
	Clobazam	ATC (N05BA09)			
	Diazepam	ATC (N05BA01)			
	Zopiclon	ATC (N05CF01)			
	Diphenhydramine	ATC (N05CM20)			
	Doxylamine	ATC (N05CM21)			
	Medazepam	ATC (N05BA03)			
	Nitrazepam	ATC (N05CD02)			
	Zolpidem	ATC (N05CF02)			
Low-value antidepressants	Amitriptyline	ATC (N06AA09)	17 (13.5)	13 (10.8)	10 (9.8)
	Amitriptylinoxide	ATC (N06AA25)			
	Doxepin	ATC (N06AA12)			
	Trimipramine	ATC (N06AA06)			
Low-value antipsychotics	Levomepromazine	ATC (N05AA02)	13 (10.3)	16 (13.3)	19 (18.6)
	Olanzapine	ATC (N05AH03)			
	Haloperidol	ATC (N05AD01)			
	Quetiapin (does not complies with the guidelines for agitation and aggression)	ATC (N05AH04) NPI[c] (≥1)			
Low-value antihypertensives	Clonidine	ATC (S01EA04, C02AC01)	12 (9.5)	9 (7.5)	8 (7.8)
	Doxazosin	ATC (C02CA04)			
	Methyldopa	ATC (C02AB01)			
Low-value spasmolytics	Solifenacin	ATC (G04BD08)	7 (5.6)	5 (4.2)	6 (5.9)
	Tolterodine	ATC (G04BD07)			
Low-value antiarrhythmics	Acetyldigoxin	ATC (C01AA02)	4 (3.2)	4 (3.3)	2 (2.0)
	Flecainide	ATC (C01BC04)			
	Sotalol	ATC (C07AA07)			

(Continues)

TABLE 1 (Continued)

Lvm by active substance class[a]	Active substance (further condition)	Data requierements[b]	PwD receiving LVM		
			At baseline $n = 126$, n (%)	After 12 months $n = 120$, n (%)	After 24 months $n = 102$, n (%)
Low-value muscle relaxants	Baclofen	ATC (M03BX01)	2 (1.6)	2 (1.6)	1 (1.0)
	Tetrazepam	ATC (M03BX07)			
Low-value antiemetics	Dimenhydrinate	ATC (A04AB02)	1 (0.8)	–	–

Abbreviations: ATC, anatomical therapeutic chemical; Lvm, low-value medications; MMSE, Mini-Mental State Examination, range 0–30, higher score indicates better cognitive function; NPI, Neuropsychiatric Inventory, score ≥ 5 indicates clinically relevant symptoms; PwD People with Dementia.
[a]According to DGPPN & DGN (2017) [32], Holt, S. et al. (2010) [33], DGIM (2019) [34].
[b]Beyond demographic data (e.g., age).
[c]Score for agitation and aggression.

Sensitivity analyses were performed using multiple regression models for the most frequent Lvm cluster of drugs, that is, low-value antiphlogistics and analgesics, antidementia drugs, sedatives and hypnotics, antidepressants, and antipsychotics. The cluster of Lvm was implemented as independent variables (received vs. not received within 24 months), and all models were adjusted as described above. All statistical analyses were conducted with STATA/IC software, version 16.[38]

3 | RESULTS

3.1 | Sociodemographic and clinical characteristics at baseline

Table 2 summarizes the participants' baseline characteristics. PwD who received Lvm at baseline were slightly younger, more likely female, more depressed, and more affected by polypharmacy and potential drug interactions compared to PwD who received no Lvm treatments at baseline. There were no significant differences for any other variables.

3.2 | Prevalence of Lvm

Over 24 months, more than every second PwD ($n = 182$, 52%) received Lvm at least once. Sixteen percent of PwD ($n = 56$) received Lvm continuously over 24 months, whereas 48% ($n = 170$) did not receive any Lvm, indicating that another 126 (36%) received Lvm sporadically but not continuously over 24 months. More than 90% of those receiving Lvm at baseline were on nonrecommended antiphlogistics and analgesics ($n = 43$, 34%), sedatives, and hypnotics, such as benzodiazepines ($n = 22$, 18%), low-value antidepressants ($n = 17$, 14%), or nonguideline medications for dementia ($n = 32$, 25%). Lvm prevalence decreased over time from 36% ($n = 126$) at baseline to 34% ($n = 124$) and 29% ($n = 102$) after 12 and 24 months, respectively. Sensitivity analyses revealed no statistically significant differences between the intervention and control groups (Tables S5 and S6). Figure 1 demonstrates the trajectories of Lvm intake over time.

3.3 | Description of outcomes at baseline and after 12 and 24 months

At baseline, PwD receiving Lvm had lower mental (50–52 vs. 55, $p = 0.011$) and physical HRQoL (39–42 vs. 43, $p = 0.077$), were more likely to be hospitalized (up to 45% vs. 28%, $p = 0.029$) and incurred higher costs (up to €12,008 vs. €7052, $p = 0.001$) than those not receiving Lvm. Decreasing physical HRQoL 24 months after baseline was more pronounced in PwD receiving Lvm than in PwD not receiving Lvm (−6.1% vs. −3.5%), with the greatest decrease in PwD taking Lvm continuously over 24 months (−8.3%).

Hospitalizations increased more intensively in patients who took Lvm at least once (from 24% to 42%; +77%) or over 1 year (from 30% to 54%) than in PwD not taking Lvm (from 28% to 35%; +26%). PwD continuously taking Lvm already had a very high hospitalization rate at baseline (46%), which slightly decreased to 38% (−19%) 24 months after baseline; this decrease was also reflected in the health care costs.

PwD receiving Lvm briefly had a greater increase in health care costs over time (Lvm once: +€8919; Lvm over 1 year (+€2573) compared with those not receiving Lvm (+€355). PwD continuously taking Lvm over 24 months already had twice as high costs at baseline compared to those without Lvm (€12008 vs. €7052, $p \leq 0.001$), which slightly decreased over time (−730€). Group differences over time are summarized in Table 3 and Table S7.

3.4 | Impact of Lvm on quality of life, hospitalization and costs

Lvm (receipt vs. nonreceipt) had a significant, negative impact on patients' physical HRQoL ($b = -1.55$; 95% CI, −2.76 to −0.35; $p = 0.011$), subsequently decrease more intensively the longer that the Lvm intake was. Compared to PwD who did not receive Lvm, continuous Lvm intake over 24 months caused a lower physical HRQoL ($b = -3.35$; 95% CI, −6.73 to −0.02; $p = 0.051$) than patients receiving Lvm only once ($b = -1.85$; 95% CI, −3.47 to −0.24; $p = 0.024$). Sensitivity analyses indicated that low-value antiphlogistics/analgesics ($b = -3.41$; 95% CI, −5.15 to −1.67; $p < 0.001$) and sedatives/ hypnotics ($b = -3.11$; 95% CI, −5.42 to −0.80; $p = 0.008$) significantly

TABLE 2 Socio-demographic and clinical sample characteristics at baseline.

	Total sample	PwD receiving Lvm		
		Yes	No	
	n = 352	*n* = 126 (35.8%)	*n* = 226 (64.2%)	*p*-Value*
Age				
Mean (SD)	80.2 (5.3)	79.3 (5.0)	80.7 (5.4)	**0.022**[a]
95% CI	(79.6–80.7)	(78.4–80.2)	(80.0–81.4)	
Sex, *n* (%)				
Female	215 (61.1)	86 (68.3)	129 (57.1)	**0.041**[b]
95% CI	(56.0–66.2)	(60.1–76.4)	(50.6–63.6)	
MMSE				
Mean (SD)	22.4 (5.1)	22.8 (4.2)	22.1 (5.5)	0.241[a]
95% CI	(21.9–22.9)	(22.1–23.6)	(21.4–22.9)	
Living situation, *n* (%)				
Alone	178 (50.6)	69 (54.8)	109 (48.2)	0.267[b]
95% CI	(45.3–55.8)	(46.0–63.5)	(41.7–54.8)	
No. of ICD-10 diagnoses				
Mean (SD)	14.0 (7.8)	14.4 (7.7)	13.8 (7.9)	0.469[a]
95% CI	(13.2–14.8)	(13.1–15.8)	(12.8–14.8)	
No. of drugs taken				
Mean (SD)	7.4 (3.5)	8.6 (3.9)	6.7 (3.1)	**<0.001**[a]
95% CI	(7.0–7.7)	(7.9–9.3)	(6.3–7.1)	
Patients with polypharmacy[c], *n* (%)				
Polypharmacy	290 (83.4)	115 (91.3)	175 (77.4)	**<0.001**[b]
95% CI	(78.4–86.4)	(86.3–96.2)	(72.0–82.9)	
No. of potential drug interactions				
Mean (SD)	0.6 (0.9)	0.8 (1.0)	0.5 (0.8)	**0.007**[a]
95% CI	(0.5–0.7)	(0.6–1.0)	(0.4–0.6)	
Charlson Score				
Mean (SD)	3.4 (2.3)	3.3 (2.2)	3.4 (2.3)	0.675[a]
95% CI	(3.1–3.6)	(2.9–3.7)	(3.1–3.7)	
B-ADL				
Mean (SD)	3.5 (2.5)	3.4 (2.1)	3.6 (2.7)	0.417[a]
95% CI	(3.3–3.8)	(3.0–3.8)	(3.3–4.0)	
GDS				
Mean (SD)	3.1 (2.3)	3.5 (2.7)	2.9 (2.0)	**0.016**[a]
95% CI	(2.8–3.3)	(3.0–3.9)	(2.6–3.1)	

Note: *p*-Values less than 0.05 are highlighted in bold.
Abbreviations: B-ADL Bayer-Activities of Daily Living Scale, range 0–10, lower score indicates better performance; GDS Geriatric Depression Scale, sum score 0–15, score ≥6 indicates depression; ICD, International Statistical Classification of Diseases and Related Health Problems; Lvm, low-value medications; MMSE Mini-Mental State Examination, range 0–30, higher score indicates better cognitive function; PwD, people with dementia; SD standard deviation.
[a]Differences in means: *t*-Test two-tailed.
[b]Differences in proportions: Fisher's exact tests.
[c]Defined as ≥ 5 prescribed medications.
*Referring to PwD who received no Lvm versus at least one Lvm.

TABLE 3 Outcome-related group differences at baseline, 12 months, and 24 months among PwD who never received low-value medications, received low-value medications once in 24 months, received low-value medications for 1 year, or received low-value medications for 2 years.

	Baseline			After 12 mo					After 24 mo				
Mental HRQoL (SF-12-MCS)	**Mean (SD)**	**95% CI**	***p*-Value**	**Mean (SD)**	**95% CI**	**Δ[c] in %**	***p*-Value**		**Mean (SD)**	**95% CI**	**Δ[d] in %**	***p*-Value**	
Never, $n = 170$ (48%)	54.5 (7.7)	(53.2–55.6)	**0.011**[b]	54.7 (7.4)	(53.6–55.8)	+0.4	0.140[b]		55.0 (7.7)	(53.8–56.1)	+0.9	0.177[b]	
Once in 24 months, $n = 72$ (20%)	51.8 (10.3)	(49.4–54.2)		52.3 (10.3)	(49.9–54.7)	+1.0			53.0 (9.3)	(50.8–55.1)	+2.3		
Over 1 year, $n = 54$ (15%)	50.0 (9.8)	(47.4–52.6)		53.9 (7.3)	(51.9–55.8)	+7.8			52.6 (9.4)	(50.1–55.1)	+5.2		
Over 2 years, $n = 56$ (16%)	52.3 (10.6)	(49.6–55.1)		52.5 (9.0)	(50.1–54.9)	+0.4			53.3 (9.7)	(50.7–55.8)	+1.9		
Physical HRQoL (SF-12-PCS)	**mean (SD)**	**95% CI**	***p*-Value**	**mean (SD)**	**95% CI**	**Δ[c] in %**	***p*-Value**		**mean (SD)**	**95% CI**	**Δ[d] in %**	***p*-Value**	
Never, $n = 170$ (48%)	42.8 (10.5)	(41.2–44.4)	0.077[b,*]	42.9 (9.6)	(41.4–44.3)	+0.2	**0.003**[b]		41.3 (9.9)	(39.8–42.8)	−3.5	**0.002**[b]	
Once in 24 months, $n = 72$ (20%)	41.7 (10.1)	(39.3–44.0)		41.2 (8.7)	(39.2–43.2)	−1.2			39.2 (10.2)	(36.9–41.6)	−6.0		
Over 1 year, $n = 54$ (15%)	40.9 (9.7)	(38.4–43.5)		38.6 (10.8)	(35.7–41.5)	−5.6			39.3 (9.0)	(36.9–41.7)	−3.9		
Over 2 years, $n = 56$ (16%)	38.7 (9.7)	(36.2–41.3)		37.9 (11.9)	(34.8–41.1)	−2.1			35.5 (10.6)	(32.7–38.3)	−8.3		
Hospitalization	**yes, *n* (%)**	**95% CI**	***p*-Value**	**yes, *n* (%)**	**95% CI**	**Δ[c] in %**	***p*-Value**		**yes, *n* (%)**	**95% CI**	**Δ[d] in %**	***p*-Value**	
Never, $n = 170$ (48%)	47 (27.7)	(20.9–34.4)	**0.029**[a]	56 (32.9)	(25.9–40.0)	+19.1	0.174[a]		59 (34.7)	(27.5–41.9)	+25.5	0.093[a,*]	
Once in 24 months, $n = 72$ (20%)	17 (23.6)	(13.8–33.5)		20 (27.8)	(17.4–38.2)	+17.6			30 (41.7)	(30.2–53.1)	+76.5		
Over 1 year, $n = 54$ (15%)	16 (29.6)	(17.4–41.9)		25 (46.3)	(33.0–59.6)	+56.3			29 (53.7)	(40.4–67.0)	+81.3		
Over 2 years, $n = 56$ (16%)	26 (46.4)	(33.3–59.5)		20 (35.7)	(23.1–48.3)	−23.1			21 (37.5)	(24.8–50.2)	−19.2		
Healthcare costs	**mean (SD)**	**95% CI**	***p*-Value**	**mean (SD)**	**95% CI**	**Δ[c] in €**	***p*-Value**		**mean (SD)**	**95% CI**	**Δ[d] in €**	***p*-Value**	
Never, $n = 170$ (48%)	7052 (7458)	(5927–8177)	**0.001**[b]	7461 (7862)	(6275–8647)	+409	0.328[b]		7407 (6807)	(6380–8433)	+355	**0.008**[b]	
Once in 24 months, $n = 72$ (20%)	7483 (7848)	(5664–9302)		9007 (16,538)	(5175–12,841)	+1524			16,402 (36,725)	(7890–24,915)	+8919		
Over 1 year, $n = 54$ (15%)	7916 (6825)	(6089–9742)		11,069 (21,695)	(5263–16,876)	+3153			10,489 (12,545)	(7132–13,847)	+2573		
Over 2 years, $n = 56$ (16%)	12,008 (10,744)	(9185–14,832)		9056 (7167)	(7173–10,940)	−2952			11,278 (13,014)	(7858–14,698)	-730		

Note: p-Values less than 0.05 are highlighted in bold.

Abbreviations: CI confidence interval; HRQoL health-related quality of life; Lvm, low-value medications; PwD, people with dementia; SD standard deviation; SF-12 Short Form Health Survey mental/physical dimension, range 0-100, higher score indicates better quality of life.

[a]Differences in proportions: Kruskal-Wallis test.

[b]Differences in means: oneway analysis of variance (ANOVA).

[c]difference between baseline and 1 year after.

[d]difference between baseline and 2 years after.

[*]$p = < 0.1$.

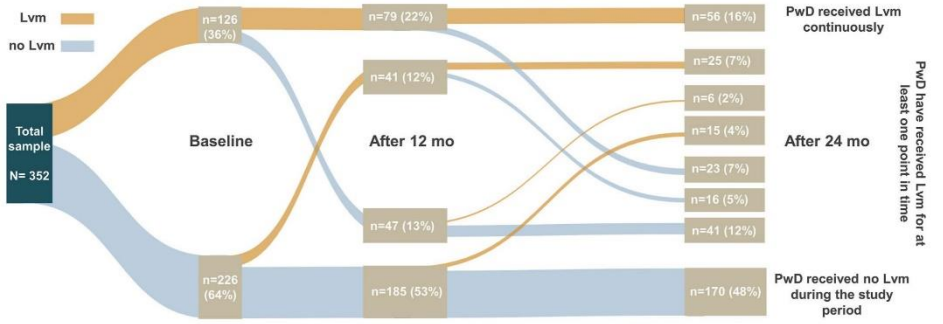

FIGURE 1 Trajectories of Lvm over 24 months. Lvm, low-value medications; PwD people with dementia; mo, months.

reduced patients' physical HRQoL. The impact of Lvm on patients' mental HRQoL was not statistically significant.

The likelihood of hospitalizations significantly increased for patients receiving Lvm (receipt vs. nonreceipt) (OR = 1.49; 95% CI, 1.06–2.09 OR; $p = 0.011$). According to the intensity of Lvm intake and compared to PwD not receiving Lvm, Lvm intake over 1 year had a significantly higher impact on hospitalization (OR = 2.61; 95% CI, 1.22–5.56 OR; $p = 0.013$) than in those receiving Lvm only once over 24 months (OR = 1.61; 95% CI, 1.09–2.36 OR; $p = 0.016$). Taking Lvm continuously over 2 years was not significantly associated with increased adjusted odds of hospitalization. The likelihood of hospitalization was significantly affected by low-value antipsychotics (see sensitivity analyses).

Lvm intake overall and once every 24 months increased medical health care costs ($b = €6810$; 95% CI, −707–14,327; $p = 0.076$; and $b = 8421$; 95% CI, €−69–€16,911; $p = 0.052$; respectively) due to significantly higher hospitalization costs. Health care costs increased with a longer duration of Lvm intake (once: €8421 over 1 year: €11,598; continuously over 2 years: €11,871). Sensitivity analyses confirmed that low-value antiphlogistics/analgesics ($b = €10,282$; 95% CI, 4068–16,497; $p = 0.001$) were the main cause of higher health care costs. Table 4 and Table S8 summarize the results of the multiple regression and sensitivity analyses.

4 | DISCUSSION

This longitudinal study provides valuable evidence about the prevalence of explicitly nonrecommended medications, which are unlikely to benefit patients and could potentially harm them, and their impacts on patient- and health care system-relevant outcomes over 24 months. Fifty-two percent of PwD received Lvm within 2 years, confirming that Lvm are highly prevalent in dementia care. The percentage of PwD receiving Lvm decreased from 36% at baseline to 29% 2 years after baseline, which could be explained by increased attention due to potential adverse drug events. The longitudinal analyses provided for the first time evidence that Lvm decreases physical HRQoL and increases hospitalizations and, hence, costs. HRQoL decline was more pronounced with continuous Lvm intake. In contrast, a sporadic Lvm intake caused a much greater increase in hospitalizations and direct medical care costs than taking Lvm continuously, which could indicate saturation (ceiling effect), implied by a very high hospitalization rate at baseline.

The prevalence of PwD receiving Lvm over time aligns with previous findings presenting a decreasing prevalence over time.[39,40] Given the potential harm of Lvm, this decrease over time could be explained by patients perceived impairments in physical functioning, such as frequent falls. Otherwise, the increased risk of hospitalization could also be perceived by physicians reevaluating prescribed medications after the increased switch between outpatient and inpatient care.

The revealed negative effects of Lvm on physical HRQoL, hospitalizations and health care costs extend previous cross-sectional findings.[15,16] The decrease in patients' physical HRQoL was greater when the Lvm were taken. A retrospective cohort study in PwD demonstrated that each additional drug increased the risk of adverse outcomes, such as mortality or hospitalization.[14] While the number of drugs remained constant for PwD without Lvm, among those with Lvm, it increased on average by one after 24 months. Additionally, Lvm themselves could drive the effect. Antipsychotics and benzodiazepines accounted for 32% of the captured Lvm in this study. Previous studies have underscored especially the increased risk of falls and, thus, the risk of hospitalizations associated with antipsychotics and benzodiazepines among PwD, which could affect self-perceived health.[41,42] The performed sensitivity analyses support these findings, indicating significantly lower physical HRQoL caused by sedatives and hypnotics, including benzodiazepines, and an increased hospitalization risk due to low-value antipsychotics. Our findings suggest a requirement of close patient monitoring by primary care physicians if Lvm are prescribed due to their shortened scope of action as second-line therapies.

The increased hospitalization risk was higher for those who received Lvm for only 1 year (161%) than for PwD taking Lvm continuously over 2 years (60%). PwD who received Lvm continuously demonstrated the

TABLE 4 Impact of low-value medications on quality of life, hospitalizations, and healthcare costs.[a]

	Treatment effect										
	PwD receiving Lvm			Intensity of Lvm intake (cumulative effect)							
	Yes			Once in 24 months			1 Year			1 Year	
Outcome variable	*b*	95% CI	*p*-Value	*b*	95% CI	*p*-Value	*b*	95% CI	*p*-value	*b*	95% CI	*p*-Value
Health-related quality of life												
Mental HRQoL (SF-12-MCS)	−0.38	−1.51–0.75	0.507	−0.33	−1.68–1.01	0.625	−0.61	−3.61–2.39	0.692	−0.07	−3.47–3.33	0.968
Physical HRQoL (SF-12-PCS)	−1.55	−2.76–−0.35	**0.011**	−1.85	−3.47–−0.24	**0.024**	−0.95	−3.71–1.80	0.498	−3.35	−6.73–0.02	0.051*
Hospitalization												
In-hospital treatment	1.49[c]	1.06–2.09[c]	**0.022**	1.61[c]	1.09–2.36[c]	**0.016**	2.61[c]	1.22–5.56[c]	**0.013**	1.60[c]	0.65–3.95[c]	0.309
Healthcare costs from payers' perspective[b]												
Medical care costs[b]	6810	−707–14,327	0.076*	8421	−69–16,911	0.052*	11,598	−11,371–34,566	0.322	11,871	−13,125–36,867	0.352
Physicians[b]	−37	−124–49	0.399	0.3	−87–88	0.995	−53	−401–295	0.765	37	−308–382.1	0.832
In-hospital[b]	6953	−546–14,451	0.069*	7893	−762–16,549	0.074*	11,067	−11,046–33,180	0.327	10,832	−13,646–35,310	0.386
Medications[b]	−227	−496–41	0.097*	268	−32–567	0.080*	59	−840–958	0.897	449	−576–1475	0.390
Medical aids[b]	−5	−182–172	0.955	−69	−201–64	0.311	−48	−709–613	0.886	−58	−781–665	0.876
Therapies[b]	101	−37–238	0.152	112	−15–239	0.083*	−28	−292–235	0.832	188	−180–556	0.317

Note: p-Values less than 0.05 are highlighted in bold.

Abbreviations: *b*, observed coefficient; CI confidence interval; HRQoL, health-Related Quality of Life; Lvm, low-value medications; PwD, people with pementia; SF-12 Short Form Health Survey mental/physical dimension, range 0-100, higher score indicates better quality of life.

[a]Multiple panel data regression models; standard errors were estimated with a nonparametric bootstrapping (2000 replications) Models were adjusted for socio-demographic and clinical variables: age, sex, dementia diagnosis (ICD-10: F00, F01, F02, F03, G30), functional impairment (B-ADL), depression (GDS), comorbidities (CCI), number of ICD-10 diagnoses, polypharmacy (≥ 5 prescribed medications), number of potential drug interactions, the respective baseline outcome values and a lagged Lvm variable.

[b]Difference between baseline and 2 years after.

[c]Odds ratio (95% CI).

*$p = < 0.1$.

highest hospitalization rate (46%) at baseline with limited potential to increase, indicating saturation (ceiling) effects. While PwD with a continuous Lvm intake showed this saturation, hospitalizations of those with short-term Lvm intake increased (receiving Lvm once: +77%; 12 months Lvm intake: +81%), confirming increased hospitalizations due to Lvm.

The multivariate results also indicated increased medical care costs due to Lvm. This effect seemed primarily driven by PwD, who received Lvm once during the 24 months (€8421), while those continuously receiving Lvm showed no more significant changes (−730€ in 24 months) due to the aforementioned potential saturation (ceiling effect) already at baseline (€12,008). In particular, hospitals (€7893) contributed to the additional costs. According to Badgery-Parker et al.[43] hospitalizations increase the risks of potentially harmful downstream effects, such as using additional treatments and hospital resources, and potentially delay care for patients with greater unmet needs. Thus, our analysis suggests that Lvm result in increased hospitalizations, which are also associated with increased health care costs and decreased HRQoL. However, additional research is needed to gain evidence about the full spectrum of low-value service provision in hospital settings and the consequences for the cost and quality of care over time.

Our data strongly suggest that efforts and interventions are needed to sensitize and motivate prescribers to review and, if necessary, discontinue the prescription of Lvm and to use appropriate alternatives. As long as better alternatives come with additional costs, as indicated by Pohl-Dernick et al.[44] short-term incentives for relevant stakeholders to change low-value prescribing behavior (and reimbursement) are lacking. Therefore, future high-quality studies with large samples, longer follow-up times, and interdisciplinary stakeholders must identify and implement appropriate measures to change prescription behaviors. With increasing numbers of PwD and the growing socioeconomic burden on health systems worldwide, the negative effects of Lvm on patient and health system outcomes emphasize the ethical, economic, and political need for action to shift spending to higher-value resource use.[5,45]

4.1 | Limitations

Data were obtained in a rural area in northeastern Germany, potentially limiting the generalizability of the presented results. PwD with a higher functional impairment were more likely to drop-out due to death which may affect the generalizability of the presented findings for this population. Furthermore, patient-reported primary data were assessed by study nurses at patients' homes, possibly affecting their completeness and accuracy due to recall bias, especially for the assessed hospitalizations and health care costs. Additional claim data from health insurance or the possibility of linking primary and secondary data were unavailable. However, to minimize the recall bias, additional information about medication use was obtained from treating practitioners, care providers, and caregivers in proxy interviews to increase the data validity and gain information about relevant clinical dimensions not usually available from secondary data. Additionally, the SF-12, a practical and adequate instrument for PwD with an MMSE score greater than 16, was used to assess HRQoL.[46] Thirty-six PwD with scores less than 16 at baseline were included, limiting the validity of the quantification of these endpoints. The sources for classifying medications as low-value represent expert consensus and predominantly emphasize clinical rationale, while the patient perspective, that is low-value care as adverse care, could not be included in the analyses. Finally, the PRISCUS List used to classify Lvm is an explicit tool offering practical advantages for large-scale epidemiologic studies due to its directly measuring the relevant data, albeit at the price of clinical contextual factors and individual patient needs.[47,48] Thus, the prevalence of Lvm may have been overestimated since some prescriptions might have been classified as Lvm, although the health service provision was clinically adequate for certain reasons, illustrating a conflict regarding specificity and sensitivity, as described by Schwartz et al.[8]

5 | CONCLUSION

This longitudinal analysis adds crucial evidence regarding Lvm in dementia, demonstrating a negative impact of Lvm on patient-reported HRQoL, hospitalizations, and direct health care costs. While continuous use of Lvm had an increasingly negative impact on patients' HRQoL with saturation effects on hospitalizations and costs already at baseline, receiving Lvm sporadically or for 1 year was relevant regarding further increases in hospitalizations and costs. Adequate alternative treatments are needed as early as possible in the patient journey through the health care system to avoid HRQoL-decreasing downstream effects for patients and resource-burdening for health systems. Further research is needed to develop appropriate and effective interventions to encourage prescribers to avoid Lvm in dementia care wherever possible.

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CONFLICTS OF INTEREST STATEMENT

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Statutory declaration

Die Dissertation habe ich selbständig angefertigt. Alle Hilfsmittel und Hilfen habe ich angegeben, insbesondere habe ich die wörtlich oder dem Sinne nach anderen Veröffentlichungen entnommenen Stellen kenntlich gemacht.

Einer Doktorprüfung habe ich mich bisher nicht unterzogen. Die Dissertation hat bisher weder in der gegenwärtigen noch in einer anderen Fassung weder der Rechts- und Staatswissenschaftlichen Fakultät der Universität Greifswald noch einer anderen Fakultät oder einem anderen Fachbereich oder einem ihrer bzw. seiner Mitglieder vorgelegen.

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