Aus dem Deutschen Zentrum für Neurodegenerative Erkrankungen in der Helmholz-Gemeinschaft, Standort Rostock / Greifswald (Standortsprecher: Univ.-Prof. Dr. med. Wolfgang Hoffmann, MPH) und der Abteilung für Versorgungsepidemiologie und Community Health des Institutes für Community Medicine (Direktor: Univ.-Prof. Dr. med. Wolfgang Hoffmann, MPH) der Universitätsmedizin Greifswald

Thema: Health economic analysis of comorbidities and innovative approaches for care and treatment of comorbidities in people with dementia

Inaugural – Dissertation

zur

Erlangung des akademischen

Grades

Doktor der Wissenschaften in der Medizin

(Dr. rer. med.)

der Universitätsmedizin

der Universität Greifswald

2021

vorgelegt von: Anika Rädke

geb. am: 19.08.1987

in: Waren (Müritz)

Dekan/in: Prof. Dr. med. Karlhans Endlich

1. Gutachter/in: Prof. Dr. med. Wolfgang Hoffmann, MPH

2. Gutachter/in: Prof. Dr. med. Hans-Helmut König, MPH

Ort, Raum: Greifswald, Ellernholzstraße 1-2, online (per Zoom-Konferenz)

Tag der Disputation: 22.11.2021

Overview of the articles

This thesis is based on the results of the DelpHi-MV study (Dementia: life- and person-centered help in Mecklenburg-Western Pomerania) and consists of two articles published in the following peer-reviewed journals:

1.) Kaczynski A, Michalowsky B, Eichler T, Thyrian JR, Wucherer D, Zwingmann I, Hoffmann W. Comorbidity in Dementia Diseases and Associated Health Care Resources Utilization and Cost. J Alzheimers Dis. 2019; 68(2):635-646. doi: 10.3233/JAD-180896.

2.) Rädke A, Michalowsky B, Thyrian JR, Eichler T, Xie F, Hoffmann W. Who benefits most from collaborative dementia care from a patient and payer perspective? A subgroup cost-effectiveness analysis. J Alzheimers Dis. 2020; 74(2):449-462. doi: 10.3233/JAD-190578.

Figures and tables

List of abbreviations

ADL	Activities of daily living
AUC	Area under the curve
B-ADL	Bayer Activities of Daily Living Scale
CCI	Charlson Comorbidity Index
CEAC	Cost-Effectiveness Acceptability Curves
CI	confidence interval
DCM	Dementia Care Management
DelpHi-MV	Dementia: life- and person-centered help in Mecklenburg-Western Pomerania
GDS	geriatric depression scale
GLM	Generalized Linear Model
GP	general practitioner
HRQoL	Health related Quality of life
ICD-10	International statistical Classification of Diseases and related health problems, 10. Revision
ICER	incremental cost-effectiveness ratio
MICE	Multiple Imputation by Chained Equations
MMSE	Mini-Mental State Examination
NMB	Net monetary benefit
SE	Standard Error
SF-6D	Six-dimensional health state short form
SF-12	12-Item short form health survey
PwD	people with dementia
QALY	Quality adjusted life years
WTP	Willingness to pay

Content

Introduction

Background

Due to demographic changes, medical and nursing care in Germany face new challenges. The effect of "double aging" [1], characterized by a declining birth rate and a dramatically increasing life expectancy, cause the aging of our society [2]. This is particularly evident in structurally weak regions, such as Mecklenburg-Western Pomerania [3]. Despite an absolute decrease in the population in Mecklenburg-Vorpommern over the next three decades, an increase in the share of people aged 65 or over in the total population from 21% in 2013 of up to 33% in 2060 is expected [4]. In addition, the accessibility of primary care is becoming more difficult in structurally weak regions. In primary care, the general practitioner (GP) usually is the gatekeeper of treatment and care. In some rural areas, there is an health care provision rate of less than 90% [5, 6]. Thus, in times of an aging population, a higher primary care capacity is needed to maintain an adequate level of treatment and care for everyone in the population, especially in structurally weak regions [7, 8].

At the same time, the aging of the population is associated with an increase in age-associated diseases including dementia [9]. The prevalence of dementia in Germany is already high. It is estimated that between 6% and 9% of the over-65s are affected by dementia in all industrialized countries. At present, about 1.8 million people in Germany have dementia, most of them have Alzheimer's disease [10]. This prevalence is expected to double every 20 years, reaching more than 3 million people with dementia by 2050 [11]. Dementia diseases are also associated with substantial healthcare costs [12, 13]. In Germany, the cost of dementia care amounts to 10.5 billion euros, which corresponds to 8.4% of the total cost of care for the over 65s [14]. The expected increasing number of people with dementia (PwD) will be associated with high health expenditures and shows the social challenge for the health care system [15, 16], highlighting that dementia is currently and will be soon one of the economically most challenging disease of older age [17, 18].

Besides, aging of the population also results in an increased number of persons with multiple diseases [19, 20]. There is an association between increasing age and increasing morbidity of the patients. Therefore, more and more patients will be multi-morbid in the next decades, having several co-existing conditions that affect treatment and care [9]. Comorbidity (i.e. one or more diseases in addition to the underlying disease) is very common, especially in older patients [21, 22]. In the age group over 60, the prevalence of comorbidity valued between 55% and 98%

[23]. The probability of multiple illnesses increases with age and is a rising problem for affected patients, their relatives, and the health care system. Comorbid patients have a higher risk of developing dementia and other cognitive disorders [24], have a reduced quality of life, need usually more care, and utilize more health care services [25-27]. In a retrospective cohort study by Mondor et al. 2017 among 30,112 long-stay home care clients with dementia, 89% of PwD were comorbid, i.e. in this population, two or more diseases were diagnosed in addition to the dementia diseases [28]. This study furthermore revealed that the risk for hospitalization and visits to the emergency room significantly increases with increasing comorbidity. The coexistence of other diseases next to dementia caused significantly higher medical care costs as well [29]. However, to my knowledge the cost of individual morbidity patterns in PwD has not been studied in the literature so far.

As pointed out, comorbidity is the rule rather than the exception in PwD. The most common comorbidities in dementia (occurring in more than 10% of patients) are high blood pressure, osteoarthritis, hypercholesterolemia, diabetes mellitus, coronary artery disease, and depression [26, 28, 30, 31]. The coexistence of chronic diseases and comorbidity in PwD frequently creates complex treatment and care challenges. Certain diseases, such as stroke and diabetes, can lead to a faster cognitive decline [32, 33]. The increasing cognitive impairment can also hinder a patient's ability to monitor concomitant diseases, comply with therapies, or communicate signs and symptoms of complications to healthcare providers, which can lead to adverse treatment and care outcomes in PwD [20].

To overcome these challenges, innovative care approaches are currently being sought to support the increasing number of PwD adequately. One way to achieve the required performance capacity is the introduction of new care concepts and structured, person-centered treatment programs for PwD [34, 35]. These approaches can relieve individual service providers, like GPs, and thus compensate for the impending shortage of supply [36, 37]. Implementing new interprofessional care programs and redistributing the responsibilities in primary care may be one approach to ensure and improve the life as well as the treatment and care situation of PwD, especially in rural areas [38, 39].

Collaborative Dementia Care Management (DCM) demonstrated with the concept of support GPs by specifically qualified nurses an adequate and effective approach for the compensation of supply deficits in the primary care sector [39-41]. The focus of this care concept is a structured treatment program, which is initiated and coordinated through specially-qualified

nurses [37]. These nurses identified PwD and their caregivers' unmet needs and initiated treatment and care needed to meet the existing needs. Simultaneously, PwD and their close relatives were much better integrated into the existing health care system without creating redundant structures. The study of Reilly et al. 2015 demonstrated that collaborative care management programs could reduce hospitalizations and the length of hospital stays, may postpone institutionalization, alleviate behaviour disturbance and depression, and improve social support for patients and caregivers [42].

However, there are solely a few studies that evaluated the cost-effectiveness of such collaborative programs. Most of them revealed inconclusive evidence concerning the cost-effectiveness [42-47]. In the face of continuous increases of healthcare expenditures and limited health care resources in many rural areas, health economic evaluations of innovative care approaches are needed. These new care concepts can only be implemented in routine care if a positive cost-benefit and/or cost-effectiveness ratio can be achieved for the involved stakeholders and patients [48]. In order to evaluate a comprehensive care concept, it is necessary to examine the costs of care depending on the (un-)met care needs, sociodemographic and clinical characteristics of the patients. Especially patients` socio-demographic and clinical characteristics, like co-existing illnesses next to dementia, could result in very different cost-effectiveness conclusions. Even though most of the economic analyses of collaborative models of care revealed inconclusive evidence concerning the cost-effectiveness, there will be sub-groups of PwD that benefit most from any such program, resulting in higher cost-effectiveness of such programs. However, knowledge about important subgroups that benefits most from innovative care models in dementia is lacking.

Objectives and research question

Little is known about comorbidity in dementia diseases and associated utilization of health care resources and cost in community-dwelling PwD. Also, there is a lack of evidence regarding the socio-demographic and clinical characteristics of patients (especially their comorbidity) that may increase the cost-effectiveness of innovative models of care, like collaborative DCM programs.

Therefore, the aims of this dissertation are to conduct (1) a health economic analysis of the impact of comorbidities in people with dementia and (2) a subgroup cost-effectiveness analysis of a collaborative DCM as an innovative approach to support and manage treatment and care

for PwD, to study sociodemographic and clinical characteristics that are associated with benefits from the perspectives of the patients and healthcare payers.

It has been hypothesized that the costs of care for PwD vary depending on PwD comorbidity and their socio-demographic and clinical characteristics [49, 50]. Therefore, the health care costs of PwD will be calculated and the association between comorbidity and socio-demographic and clinical factors of the PwD with their health care cost will be analyzed [49].

In addition, we hypothesize that there are important subgroups (e.g. PwD with low, high or very high comorbidity and different sociodemographic characteristics) that benefit differently most from the DCM intervention. We will analyse for which subgroups the most significant effect on costs, on Quality-adjusted Life Years (QALY), and the highest individual cost-effectiveness, respectively, could be achieved.

Material and Methods

Study design and setting

The analyses were based on data from the DelpHi-MV trial, a pragmatic, GP based, cluster-randomized prospective controlled intervention trial [37]. The study aimed to implement and to evaluate the innovative concept of collaborative Dementia Care Management in Germany. The DCM was developed to support community-dwelling PwD and their caregivers in the primary care setting and to improve their treatment and care [39, 51, 52]. In this trial, DCM was operationalized as a complex intervention aiming to provide optimal individualized treatment and care for PwD and support to caregivers in close cooperation with the treating GP [39, 51, 52]. A specifically qualified nurse, so-called Dementia Care Manager, assessed and recorded all nursing, medical, psychosocial, social and legal care needs of the PwD and his or her caregiver, transferred these needs into an individualized intervention plan and subsequently implemented each intervention in close cooperation with the treating GP [39]. After six months of intervention, the intervention group was compared with the cluster-randomised control group who received usual care.

Patients were at the age of 70 years or older, community-dwelling, had been positively screened for dementia using the DemTect procedure (DemTect<9) in participating GP practices, and provided written informed consent for participation in the study. In case a patient was unable to give written informed consent, the form was signed on his or her behalf by his or her legal

representative (as approved by the Ethical Committee of the Chamber of Physicians of Mecklenburg–Western Pomerania, registry number BB 20/11).

The DelpHi-trial revealed that the DCM program increases the prescription rate of anti-dementia drugs, significantly alleviates the neuropsychiatric symptoms, and reduces caregiver burden [37, 51]. Overall, PwD who received the DCM had higher HRQoL scores and incurred lower healthcare costs compared to controls [50, 51, 53]. Effectiveness, efficiency and health economic analysis of the DCM of the DelpHi-trial have been published elsewhere [37, 50, 54].

Study population

Overall, n = 6,838 people were screened by 128 GPs and n = 1.167 (17%) PwD were eligible for the study. Out of this n=634 (54%) gave an informed consent to participate in this study and n=516 started the baseline assessment (intervention: 348 PwD; controls: 168 PwD). There were no significant differences considering age, sex, and the DemTect score among patients starting the baseline assessment (n=516) and those who dropped out before starting the baseline assessment (n=118) [55]. A detailed description of this sample is given elsewhere [56].

The *first analysis* (economic analysis of healthcare utilization of cost depending on PwD comorbidity) was based on cross-sectional data of the DelpHi-trial. 118 PwD were excluded because of missing data of relevant variables. The primary causes for missing data included were dropout due to death (n=19), withdrawal of informed consent (n=85), relocation (n=5), and other reasons (n=9). In 154 patients, the dementia diagnosis (ICD-10) could not be finally confirmed after completing the baseline assessment. These were also excluded from this analysis. Finally, the first analysis was based on cross-sectional data of 362 PwD. The study flow chart is represented in Figure 1 and shown in the attached publication in the appendix (Supplementary Figure 1). The drop out analysis, revealing that especially PwD with a higher DemTect Score, patients with a lower care level and thus with a lower need for care as well as patients with a lower Charlson comorbidity index (CCI) dropped out, is represented in the attached publication in the appendix (Supplementary Table 1 and 2) [57].

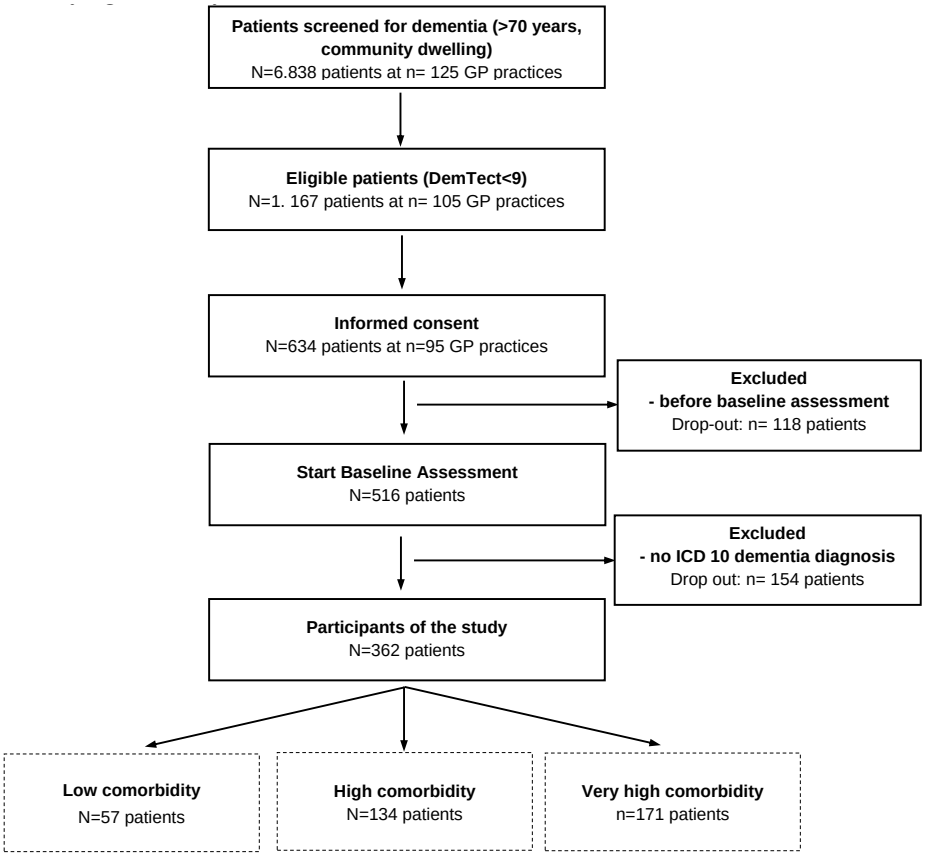

Figure 1: Study flowchart

The *second analysis* was based on 24 months longitudinal data of the DelpHi-trial. 85 participants withdrew their informed consent after completing the baseline assessment, n=73 passed away, and n=6 postponed the first and second follow-ups, resulting in a sample of 408 and 352 participants who accomplished the first and second study follow-up. Thus, the second analysis was conducted on a sample of 444 participants who received either the DCM or usual care and completed the baseline and at least one of the follow-up assessments or died before the first follow up assessment (deceased patients were included in this analysis) [58, 59].

Data assessment

In the DelpHi-MV trial, data was collected by questionnaires at baseline, and at scheduled follow-up visits after 12 months and 24 months [37]. Medical diagnoses for dementia (ICD-10 codes) and comorbidities, including the exact date of the initial diagnosis, if any, were retrieved from the patients' medical records with the permission of the treating GPs. Baseline assessment, intervention, and annual follow-ups were carried out by specifically qualified nurses, so-called dementia care managers [39, 51].

Sociodemographic and clinical factors

Sociodemographic data included age, gender, and living situation (living alone vs. not alone). The following clinical variables were assessed as well: severity of cognitive impairment, number of medications, deficits in activities of daily living (ADL), and depression. The severity of cognitive impairment was assessed by the Mini-Mental Status Test (MMST) [60], a psychometric testing procedure to categorize PwD according to the severity of their cognitive impairment, into the following categories: no indication (MMST score >26), mild (MMST score 20-26), and moderate to severe (MMSE Score 0–19) cognitive deficits [61, 62]. The MMSE is less sensitive for detecting milder forms of cognitive impairment (43%) compared to the DemTect procedure (80% to 100%) that was used for the screening in GP practices and the subsequent inclusion of patients in the trial [63, 64]. Therefore, it is possible that some patients, who were screened positive for dementia with the DemTect, are not cognitively impaired according to the MMSE (score 27 to 30). The Bayer Activities of Daily Living Scale (B-ADL) [65] was used to assess deficits in ADL. Depression was assessed using the GDS (sum score 0-15, score $\geq$ 6 indicates depression) [66].

Comorbidity of patients living with dementia

Comorbidity was identified by each patient's medical ICD-10 diagnoses listed in the GP´s medical records. In addition, the charlson comorbidity index (CCI) was used to provide a comorbidity summary score. The CCI is the most commonly used comorbidity score to measure the burden of disease in health care data and is based on medical diagnoses including the International Classification of Disease, 10th Revision (ICD-10) codes [67]. A weighted sum score of the CCI can be derived and relates to the absence and presence of different comorbid conditions [68]. All patients in our sample received a formal dementia diagnosis, and we considered sixteen diseases of the CCI for our analysis of the economic burden of comorbidity in dementia. Comorbidity was categorized in low (CCI-score=1, one comorbidity in addition to dementia), high (CCI-score=2-3, two or three comorbidities in addition to dementia) and very high comorbidity (CCI-score>3, more than three comorbidities in addition to dementia). The description of ICD-10 diagnoses included in each comorbidity level and the calculation of the CCI is represented in the attached article Nr. 1 (Supplementary Table 3) [57].

Health care utilization and health care costs

The health care resource utilization was retrospectively collected through comprehensive, standardized, computer-assisted interviews at 12 and 24 months after baseline. PwD,

caregivers, and care services staff, if available, were interviewed face to face. The utilization review comprises a list of widespread healthcare resources and services (e.g. physician visits, in-hospital treatments, medications, medical aids and therapies and ambulatory care) and collected detailed information about the frequencies of the utilization of different medical and formal care services.

The health care costs for each patient were calculated using the assessed healthcare resource utilization and published unit costs [69]. Healthcare costs were calculated from a public payer´s perspective, including all resources used that are completely attributable to the use of a healthcare intervention or illness (direct costs).

Health-related quality of life and Quality-adjusted Life Years

HRQoL was measured at baseline, follow-up one, and follow-up two using the SF-12, a generic, multidimensional instrument that measures the physical dimension of HRQoL [70]. Health utilities were derived from the SF-12 using the method of Brazier & Roberts and used to calculate QALYs for each patient separately [71]. The responses to the SF-12 were converted to health utilities using the scoring algorithm for the SF-6D, a preference-based single index measure for HRQoL anchored at 0 for death, and 1 for full health [71]. A linear decrease of HRQoL between baseline, 12 months, and 24 months was assumed, which is consistent with the clinical course of dementia diseases. In case of death, the utility value was assumed to equal zero. Individual QALYs were calculated by using the AUC technique (area under the curve) and discounted at 5% per year [69, 72-74].

Incremental cost-effectiveness and individual Net Monetary Benefit

Next to the calculation of the individual cost and QALYs, the individual net monetary benefit (NMB) was calculated as a further outcome of the *second analysis* to identify individual PwD who benefits most from a collaborative DCM. Principally, the subgroup cost-effectiveness analysis was based on the calculation of the incremental cost-effectiveness ratio (ICER). The ICER embraces the ratio of the differences in total mean costs $\bar{c}$ and total mean effects $\bar{e}$ (QALYs) between the intervention (i.e. PwD who received the DCM) and control group (i.e. PwD who received care as usual) (see formula 1) [75].

(1) $$ICER = \frac{\bar{c}_{IG} - \bar{c}_{CG}}{\bar{e}_{IG} - \bar{e}_{CG}} = \frac{\Delta\bar{c}}{\Delta\bar{e}}$$

Thus, this ratio representing the incremental cost per QALY gained by the DCM program compared with the usual care [75]. The cost-effectiveness ratio was used to calculate the NMB for each patient by assigning a monetary value to the achieved incremental benefit of the intervention group compared to the control group. The NMB is calculated as follows:

(2) $$\overline{NMB} = (\Delta\overline{e} \times \lambda) - \Delta\overline{c}$$

$\overline{NMB}$: net monetary benefit

λ: willingness-to-pay for one QALY

$\Delta\overline{e}$: incremental mean effects/ benefit

$\Delta\overline{c}$: incremental mean costs

An intervention is considered to be cost-effective if NMB is >0 [76-78]. Thus, a positive NMB represents that the intervention has more additional value than extra costs and means, that the intervention is cost-effective at a given willingness-to-pay (WTP) threshold (λ) [79].

For the analysis, we used the patient-specific net monetary benefit according to the recommendation of Ridder et al. [80] to assess the cost-effectiveness of the DCM at the individual patient level. Under this framework, each subject's NMB was defined by using the observed data on the effects and cost for the respective PwD [78-80].

Handling of missing data

Missing values were handled by using Multiple Imputation by Chained Equations (MICE). MICE was specified for each variable and adjusted for age, gender, living situation, and comorbidity [59, 81, 82]. The imputations were conducted by adding 50 additional data sets for each missing variable [53, 83].

Statistical analysis of comorbidity and cost in dementia

For the *first analysis* of the economic impact of comorbidity on health care utilization and costs in community-dwelling PwD, we used descriptive statistics for sample characteristic and the prevalence of each comorbidity. Kruskal-Wallis tests were performed to assess the statistical significance of the difference between the low, high and very high comorbidity subgroup. To analyze the associations between comorbidity and health care cost, we used multiple linear regression models with random effects for each GP. For cost for physician treatments,

hospitalization, medication, medical aids, therapies and formal care, separate linear regression models were conducted. Either the number of diseases according to CCI or the three levels of comorbidity were used as a predictor of interest separately in the models. We furthermore adjusted each model for gender, age, living situation, ADL and depression as covariates. Because of a highly skewed distribution of health care costs standard errors (SE) and confidence intervals (CI) for regression coefficients were estimated by non-parametric bootstrapping with 2,000 replications [84]. Furthermore, we conducted a sensitivity analysis to test the robustness of the results obtained by the multivariate linear regression, using a Generalized Linear Model (GLM).

Statistical analysis of subgroup cost-effectiveness analysis

The *second analysis* aimed to identify relevant subgroups who benefit most from a DCM from a patient and economic perspective. Therefore, we used the patient-specific NMB to assess the individual cost-effectiveness of the DCM at the individual patient level.

The individual NMB approach requires a selection of a cost-effectiveness ceiling ratio. A threshold of 40,000€ per individual QALY was selected for our main analysis [78]. In addition, we calculated the individual NMB with 80,000€ and 160,000€ per individual QALY.

To identify relevant subgroups that benefit most from the DCM the following subgroup-categories were used: younger (<80 years) and older PwD (80 years and older), male and female PwD, PwD living alone vs. those living not alone, PwD with low (CCI< 2), high (CCI < 3) and very high comorbidity (CCI > 3) as well as PwD with no indications (MMSE ≥ 27), mild (MMSE 20–26) and moderate to severe (MMSE 0–19) cognitive impairment and PwDs with no (BADL 1.0–2.0), mild (BADL 2.1–5.0) and high deficits (5.1–10.0) in daily living activities [85].

Cost-effectiveness analyses were conducted for each subgroup by stratifying the sample according to their socio-demographic and clinical characteristics. Within each separated subgroup the ICER was calculated using the incremental cost per QALY gained by the DCM program compared with usual care [75]. To handle sampling uncertainty in the ICER, we used non-parametric bootstrapping (1,000 resamples, stratified for cluster and group distribution) [86]. The probability of the DCM being cost-effective was calculated using the NMB and different WTP margins (0€ per QALY gained to 160,000€ per QALY gained) [87, 88]. Finally, Cost-Effectiveness Acceptability Curves (CEAC) were presented for each subgroup.

We assessed the impact of the DCM on i) individual total costs, ii) QALY and iii) PwD individual NMB by using multivariate linear regression models with random effects for the GPs. A vector of subject characteristics and interaction terms between the subject characteristics (subgroup) and the intervention indicator (intervention vs. control) were included in the linear regression models as a predictor of interest, aiming to explore if the cost-effectiveness varies over different patient subgroups. Therefore, the following interaction terms were used: Study group (intervention) with age (reference: older), sex (reference: female), living situation (reference: living alone), deficits in daily living activities using the B-ADL (reference: no deficits), cognitive deficits using the MMSE (reference: no indication of cognitive deficits), comorbidity using the CCI (reference: low comorbidity). The interaction terms with the intervention group were used to control for homogeneous effects across the single patient groups and to assign the average cost, QALYs and NMB for different patient groups [79]. All models were furthermore adjusted for study group, gender, age, living situation, MMST score, B-ADL, GDS, and CCI. We performed all statistical analyses by using the software STATA/IC 13.0 [89].

Results

Comorbidity and cost in dementia

Socio-demographic and clinical characteristics

The *first analysis* of comorbidity and associated health care resources utilization and cost is based on a sample of 362 PwD with a confirmed diagnosis of dementia. Patients were on average 81 (SD = 5.5) years old, mostly female (61.6%) and on average mildly cognitively and functionally impaired. Comorbidity was highly prevalent in the study population. 47% of PwD had a very high, 37% a high and 16% a low comorbidity in addition to dementia. The subgroup with more than three comorbidities in addition to dementia (e.g. with very high comorbidity) was more likely to be male (49%, n=84) compared to the subgroup having only one comorbidity in addition to dementia (low comorbidity) (23%; n= 13; p=0.001). The most prevalent co-existing comorbidities were diabetes mellitus (42%), peripheral vascular disease (28%), cerebrovascular disease (25%), and congestive heart failure (20%). The most expensive comorbidities in addition to dementia were moderate or severe liver disease (mean cost: 32,551€), metastatic solid tumors (11,646€), rheumatic diseases (11,348€), and renal diseases

(10,612€). The costs of all comorbidities (according to the CCI) in addition to dementia are displayed in Table 1.

Table 1: Comorbidities according to the CCI and mean costs per comorbidity in addition to dementia (Source: manuscript Nr. 1, page 640 [57])

Comorbidity[1]	**Mean costs per comorbidity in addition to dementia mean (SD) in €**
Moderate or severe liver disease	32,551 (0.0)
Metastatic solid tumor	11,646 (6,900)
Rheumatic disease	11,348 (10,158)
Renal disease	10,612 (8,850)
Congestive heart failure	10,310 (8,521)
Chronic pulmonary disease	9,958 (10,089)
Hemiplegia or paraplegia	9,588 (9,223)
Any malignancy[2]	9,528 (8,960)
Mild liver disease	8,923 (10,765)
Diabetes with chronic complication	8,771 (7,836)
Peripheral vascular disease	8,387 (9,095)
Cerebrovascular disease	8,136 (8,547)
Diabetes without chronic complication	7,877 (7,368)
Peptic ulcer disease	7,712 (9,047)
Acute myocardial infarction	6,106 (4,212)
AIDS/HIV[3]	-

[1] Comorbidities based on the Charlson comorbidity index (CCI); [2] including lymphoma and leukemia, except malignant neoplasm of skin, [3] There were no PwD with AIDS/HIV in our sample. Therefore, no costs could be determined.

The descriptive statistics of the characteristics of the total sample, as well as of the subgroups with a low, high and very high comorbidity and the prevalence of the 17 identified diseases of the CCI is described in more detail in article 1 (manuscript Nr. 1, page 639 f.) [57].

Health care utilization and Health care costs in PwD with comorbidities

The utilization of medical treatments was significantly higher in patients with a very high comorbidity compared to patients with a low comorbidity. However, PwD with high comorbidity were shorter hospitalized compared to PwD with a low or very high comorbidity. Also, the very high comorbid sample utilized more formal care than the low comorbid-sample. In contrast, the high comorbidity group utilized less formal care than the low and very high comorbid-sample. All group differences were statistically significant, except the health cure days, day/night care and ambulatory care [57].

The annual medical care costs were higher in the very high comorbidity group compared to the low comorbidity group. However, total costs for medical treatment were on average highest in the very high comorbidity group (6,601€) but lowest in the high comorbidity group (4,167€). However, the costs for medical treatment were not much higher in the low comorbidity group (4,431€). The results demonstrated that the in-hospital costs curve was u-shaped. The other cost categories of the medical treatment costs (i.e. costs for physician visits, medication and medical aids) increase with rising level of comorbidity.

In contrast, the costs for formal care were on average higher in the very high comorbidity group (2,879€) compared to the high comorbidity group (2,283€) but lower in comparison to the low comorbidity group (3,105€). Thus, the low comorbidity group showed the highest costs for formal care owing to u-shaped costs for ambulatory care and decreasing costs for day & night care with an increasing level of comorbidity.

Overall, total costs from a payer's perspective, subsuming the medical and formal care costs, were 7,536€ (SD: 10,718€) for the low comorbidity sample (n=57), 6,450€ (SD: 7,703) for the high comorbidity sample (n=132) and 9,480€ (SD: 8,666€) for the very high comorbid sample (n=171). We observed u-shaped health care costs in PwD with increasing level of comorbidity, especially due to the u-shaped costs for formal care which are not related to comorbidity. Thus, mean total health care costs were highest in patients with a very high comorbidity compared to those with a high or low comorbidity in addition to dementia. However, total health care costs were lower in PwD with a high comorbidity as in patients with a low comorbidity. All cost differences were statistically significant, except the costs for formal care [57]. A detailed description of the health care resources used for each level of comorbidity is represented in Table 2.

Table 2: Health care resource utilization and costs by level of comorbidity (n=362) (Source: manuscript Nr. 1, page 641) [57]

	Level of comorbidity			
	Low comorbidity (n=57)	**High comorbidity (n=134)**	**Very high comorbidity (n=171)**	**p-value**
Health care resource use	mean (SD)	mean (SD)	mean (SD)	**
Medical treatments				
Physician, visits	10.8 (10.2)	11.7 (8.8)	12.7 (7.8)	0.022
In-hospital, days	3.7 (10.0)	2.4 (7.9)	5.1 (9.7)	0.003
Medication, number	4.2 (2.3)	5.8 (2.8)	7.5 (3.1)	0.001
Medical aids, number	3.6 (2.6)	4.6 (2.8)	5.4 (2.7)	0.001
Rehabilitation, days	0.4 (2.8)	0.0 (0.0)	1.0 (5.8)	0.032
Health cure, days	0.0 (0.0)	0.3 (2.2)	0.3 (2.5)	0.481
Therapies, visits	5.4 (13.1)	4.7 (16.5)	4.9 (13.7)	0.015
Formal care				
Day/ night care, days	8.6 (26.6)	7.8 (38.2)	13.4 (46.8)	0.070
Ambulatory care, visits	128.8 (277.3)	99.7 (262.4)	167.1 (336.5)	0.061
Costs in Euros, mean (SD)*				
Medical treatments	**4,431 (7,113)**	**4,167 (5,531)**	**6,601 (6,724)**	**0.001**
Physicians	339 (455)	374 (374)	388 (243)	0.012
In-hospital	2,318 (6,308)	1,550 (4,867)	3,303 (6,227)	0.002
Medication	998 (1,037)	1,415 (1,365)	1,860 (1,462)	0.001
Medical aids	663 (837)	733 (873)	948 (999)	0.001
Therapies	111 (268)	95 (338)	101 (280)	0.015
Formal care	**3,105 (5,280)**	**2,283 (4,874)**	**2,879 (5,231)**	**0.041**
Day/ night care	1,191 (2,605)	1,179 (3,337)	1,124 (2,929)	0.098
Ambulatory care	1,914 (4,474)	1,104 (2,894)	1,755 (3,501)	0.066
TOTAL COST (Payer perspective)	**7,536 (10,718)**	**6,450 (7,703)**	**9,480 (8,666)**	**0.001**

*** Time period of costs: 12-month retrospective; demonstrated costs are annual mean costs per patient or patient group**

**** statistical significance of the difference between the low, high and very high comorbidity sample; Kruskal-Wallis was performed**

Associations between health care costs and comorbidity in PwD

The multivariate analysis revealed that each further comorbidity captured by the CCI significantly increases total health care costs on average by 528 € (*SE*= 214, CI_{95}=109-947€, p=0.014). Whereas there was no significant association between comorbidity and formal care costs, multivariate models observed a significant association with medical care cost. Each further comorbidity that is captured by the CCI was associated with higher medical care costs of 455€ (*SE*=174, CI_{95}=114-795, p=0.009). Looking at the comorbidity categories, a very high comorbidity was associated with 818€ (*SE*= 168, CI_{95}=489-1147, p<0.001) higher medication

costs and with 336€ (*SE*=161, CI_{95}=20-652, *p*=0.037) higher cost for medical aids, each compared with patients with a low comorbidity.

However, no significant associations between higher comorbidity and costs for physician consultations, in-hospital costs, and therapy costs as well as for formal care cost were found [57]. In the sensitivity analysis using GLM confirmed the significant association between PwD comorbidity and costs (the sensitivity analysis is described more detailed in the article).

S*ubgroup cost-effectiveness analysis*

Sample, sociodemographic and clinical data

The subgroup cost-effectiveness analysis *(second analysis)* was based on 444 participants who received either the DCM or usual care and completed the baseline and at least one of the follow-up assessments or died. Patients were on average 80 years old, mostly female (60%), half of them were living alone (51%) and were on average mildly cognitively (mean MMST: 22) and functionally impaired (mean B-ADL: 4). Overall, 39% of the total sample had a very high comorbidity (41% in the intervention group and 33% in the control group) compared to 47% in our first analysis. In 20% of the intervention group and 30% of the control group the level of comorbidity was low, whereas in 41% of the intervention group and 33% of the control group the comorbidity was very high [53]. The sociodemographic and clinical characteristics of the study population of the *second analysis* were shown in the attached article Nr. 2 (manuscript page 454) [53, 57, 90].

Cost-effectiveness of DCM in PwD with comorbidities

Comorbidity was again highly prevalent in the sample and total costs significantly increased by 528 € (*SE*=214, CI_{95}=109-947, *p*=0,014) with each further comorbidity. As demonstrated in other studies patients with comorbidity are very often underserved by poorly integrated care systems [91, 92]. Therefore, collaborative care models like DCM represent a solution to improve management and coordination of treatment and care in PwD with comorbidities and may reduce long-term costs. The following results demonstrate that the DCM intervention was most cost-effective in PwD with a high or very high comorbidity.

Incremental cost and QALYs of PwD with comorbidities

Overall and irrespectively of the sociodemographic and clinical characteristics, PwDs receiving DCM tended to incur 569€ (SE=2,491, CI_{95}= -5466 – 4328, p= 0.590) lower cost and gained

on average 0.05 (SE=0.045, CI_{95}= -0.04 - 0.14, p=0.130) more QALYs compared to care as usual over the 24 months' time period [53].

Looking at the level of comorbidity, PwD with a high comorbidity caused lower incremental costs of -7,416€ and higher QALYs of +0.07 compared to the entire sample, representing that DCM was more likely to be cost-effective in PwD with a high comorbidity. However, in PwD with a low or a very high comorbidity the ICER indicated higher incremental cost (+2,885€ and +3,497€, respectively) and lower or non-significant incremental QALYs (-0.073 and +0.131‡, respectively) for the DCM intervention as compared with care as usual, indicating a lower cost-effectiveness. We observed u-shaped cost-effectiveness ratios for the comorbidity subgroups as well. One reason might be the high costs for formal care in the low and very high comorbidity group. The cost-effectiveness plane below displays the cost-effectiveness ratios for the subgroup of PwD with low, high and very high comorbidity (Figure 2).

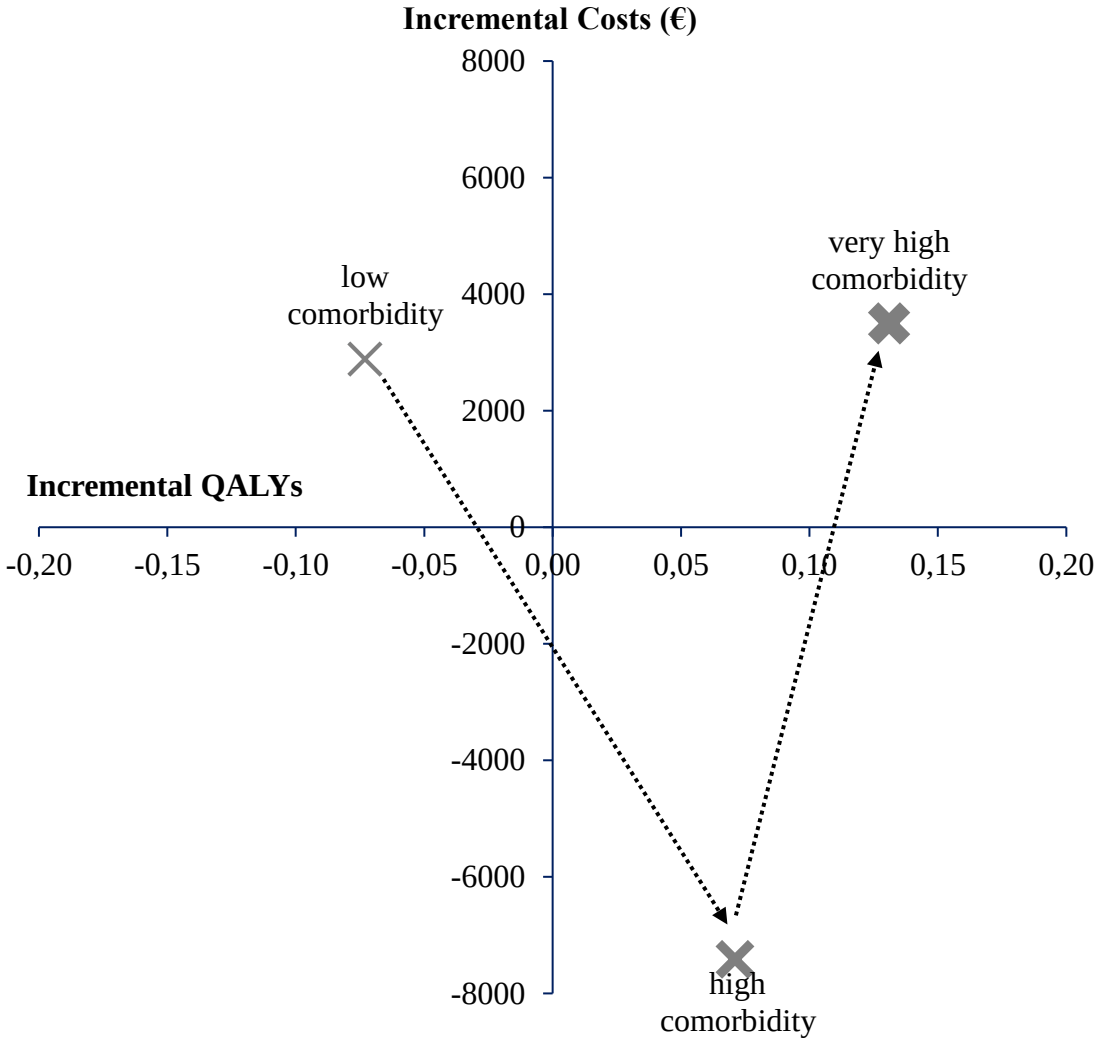

Figure 2: Cost-effectiveness plane for subgroups of comorbidity

Incremental cost and QALYs considering other sociodemographic and clinical factors

Looking at the further subgroups, for older PwD (incr. cost: -3,716€; incr. QALYs: +0.04), female PwD (incr. costs -4,307€; incr. QALYs: +0.04), and PwD living alone (incr. cost: -3,642€; incr. QALY: +0.03), the ICER for these subgroups indicated lower incremental cost and higher incremental QALYs for the DCM intervention as compared with care as usual and thus, a higher cost-effectiveness. Furthermore, the intervention was less costly (-2,678€ and -3,472€, respectively) and more effective (+0.05 and +0.16 QALY) for PwD with mild and high deficits in daily living activities (B-ADL). For the subgroup of PwD with mild and moderate to severe cognitive deficits (only a few PwD in our sample were severely cognitively impaired according to the MMSE) the incremental costs valued -648€ (mild) and -5,574€ (moderate to severe), respectively, and QALYs were +0.11 (mild) and +0.10 (moderate to severe), respectively, highlighted that DCM was more cost-effective than usual care. A description of the incremental cost and incremental QALYs of all selected subgroups is presented in Table 3.

Table 3: Description of incremental cost, effects and ICER (Source: Article Nr. 2, page 455)

	n (%)	Incremental Cost, mean (SD)	Incremental QALY, mean (SD)	ICER
Overall, total sample	444 (100%)	-569€ (2,491)	+0.049 (0.045)	DCM dominates
Comorbidity (Charlson comorbidity index)				
low	102 (23.0%)	+2,885€ (4,738)	-0.073 (0.080)	Usual Care dominates
high	171 (38.5%)	-7,416€ (4,740)	+0.071 (0.075)	DCM dominates
very high	171 (38.5%)	+3,497€ (3,410)	+0.131 (0.071)‡	26,694€/QALY
Age				
young (<80 years)	200 (45.0%)	+2,425€ (3,162)	+0.069 (0.067)	35,145€/QALY
old (>80 years)	244 (55.0%)	-3,716€ (3,701)	+0.039 (0.057)	DCM dominates
Sex				
male	177 (39.9%)	+4,911€ (3,266)	+0.069 (0.076)	71,173€/QALY
female	267 (60.1%)	-4,307€ (3,488)	+0.036 (0.052)	DCM dominates
Living situation				
living alone	224 (50.5%)	-3,642€ (3,938)	+0.034 (0.063)	DCM dominates
living not alone	220 (49.5%)	+1,799€ (3,020)	+0.067 (0.060)	26,851€/QALY
Deficits in Daily Living Activities (B-ADL)				
no	158 (35.6%)	+668€ (3,184)	+0.032 (0.057)	20,414€/QALY
mild	162 (36.5%)	-2,678€ (4,977)	+0.053 (0.070)	DCM dominates
high	124 (27.9%)	-3,472€ (3,882)	+0.159 (0.091)‡	DCM dominates
Cognitive Deficits (MMSE)				
no indication	99 (22.3%)	+5,485€ (3,055)‡	-0.147 (0.083)‡	Usual Care dominates
mild	227 (51.1%)	-648€ (3,955)	+0.109 (0.059)‡	DCM dominates
moderate to severe	118 (26.6%)	-5,574€ (4,495)	+0.102 (0.093)	DCM dominates

MMSE, Mini-Mental State Examination, Range 0-30, a higher score indicates better cognitive function; B-ADL, Bayer-Activities of Daily Living Scale, range 0-10, a lower score indicates better performance; SD, standard deviation; CI, confidence interval; ‡ p<0.01; DCM dominates: Incremental QALY and costs indicating that the dementia care management was more likely to be less costly and more effective according to QALY. For female and alone living patients with mild deficits in daily living, mild cognitive deficits and high comorbidity the incremental costs decreased but more QALY were gained. Therefore, DCM still dominates the usual care from a cost-effectiveness perspective.

Cost-effectiveness acceptability curves for the selected subgroups

Overall, at the WTP threshold of 0€ per QALY gained the probability of the DCM being cost-effectiveness was 54% for the entire sample. The probability increased to 86% and 93% at a WTP of 40,000€ and 80,000€ per QALY gained, respectively.

The probability of cost-effectiveness of the DCM was higher in PwD with high comorbidity at WTP thresholds of 40,000€ per QALY (96%) and lower in PwD with low (26%) or very high comorbidity (70%) compared to the overall sample. The CEAC for the comorbidity subgroups is represented in Figure 3. As seen in figure 3, the acceptability curve is above 0.95 for all WTP values above € 40,000 per QALY for people with high comorbidity, highlighted that the DCM is very likely to be cost-effective in PwD with high comorbidity, but unlikely in PwD with a low or very high comorbidity. As seen in our first analysis and Table 2 as well, PwD with a low and very high comorbidity received more formal care and were more often admitted to hospitals than PwD with a high comorbidity.

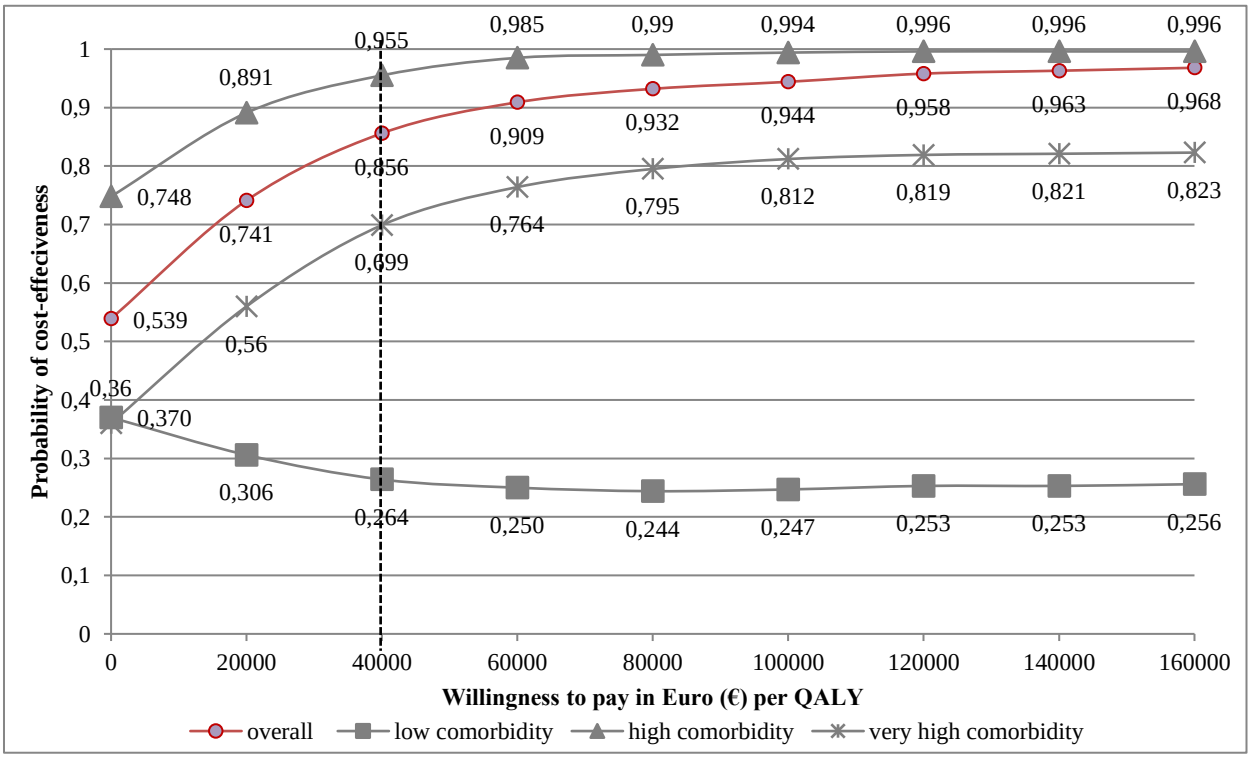

Figure 3: Cost-effectiveness acceptability curves, DCM intervention overall and subgroups of comorbidity

Table 4 represents the probabilities of cost-effectiveness over different WTP thresholds for all other selected subgroups.

Table 4: Probability of cost-effectiveness over different willingness to pay thresholds and patient subgroups

	Probability of Cost-Effectiveness at different Willingness to pay threshold (λ)								
	0	**20,000**	**40,000**	**60,000**	**80,000**	**100,000**	**120,000**	**140,000**	**160,000**
Age									
young	0.393	0.440	0.478	0.503	0.532	0.549	0.558	0.566	0.570
old	0.645	0.770	0.871	0.918	0.942	0.953	0.957	0.961	0.962
Sex									
male	0.021	0.060	0.158	0.251	0.326	0.391	0.440	0.475	0.503
female	0.863	0.935	0.959	0.973	0.979	0.981	0.981	0.975	0.975
Living situation									
living alone	0.819	0.928	0.962	0.983	0.988	0.991	0.991	0.991	0.990
living not alone	0.134	0.203	0.263	0.327	0.308	0.411	0.440	0.465	0.479
Deficits in Daily Living Activities (B-ADL)									
no	0.241	0.184	0.161	0.15	0.151	0.153	0.164	0.166	0.175
mild	0.513	0.595	0.687	0.752	0.794	0.825	0.845	0.861	0.869
high	0.625	0.919	0.966	0.977	0.984	0.986	0.988	0.989	0.99
Cognitive Deficits (MMSE)									
no indication	0.180	0.064	0.027	0.021	0.020	0.019	0.023	0.022	0.022
mild	0.464	0.631	0.763	0.845	0.869	0.893	0.904	0.906	0.914
moderate to severe	0.927	0.985	0.996	0.996	0.996	0.996	0.996	0.997	0.996

For PwDs older than 80 years, the probability of the DCM being cost-effective was much higher compared to the younger PwD (<80 years) at the WTP of 40,000€ per QALY gained (87% vs. 48%, respectively). In addition, the probability that the intervention is cost-effective was very high in females compared to males at the WTP of 40.000€ per QALY gained (96% vs. 16%, respectively). Furthermore, the probability of cost-effectiveness was much higher in PwD living alone at the WTP threshold of 40,000€ per QALY (96% vs. 26%, respectively) compared to PwD not living alone. Comparing PwD without deficits in ADL, the probability of cost-effectiveness was higher in PwD with high deficits in ADL at a WTP threshold per QALY of 40,000€ (97% vs. 16%, respectively). Concerning the severity of cognitive impairment, the probability of cost-effectiveness was higher in PwD with moderate to severe cognitive deficits at a WTP threshold of 40,000€ per QALY (100% vs. 3%, respectively) compared to PwD with no indication of cognitive deficits.

In summary, the probabilities of cost-effectiveness revealed that between the identified subgroups based on one single property, patients with a high comorbidity (96%) and moderate cognitive deficits (99%), female PwD (96%) and PwD living alone (96%) indicated the highest probability that the DCM intervention is cost-effective at the WTP of 40,000€ per QALY gained [90].

Association between interaction terms and individual net monetary benefit

Concerning the individual NMB with λ=40,000€, the multivariate analyses confirmed a significant interaction effect between female PwD (b=+11,733; SE=3,721) and PwD living alone (b=+8,417, SE=3,676) receiving the DCM. Those subgroups had a higher individual NMB, demonstrating that the DCM was more likely cost-effective in these subgroups. In addition, PwD with mild cognitive (b=+13,456, SE=4,657) and moderate cognitive deficits (b=+12,621, SE=5,279) who received the DCM had significantly higher individual NBM over the 24 months' time horizon compared to mild and moderate cognitively impaired PwDs receiving care as usual. The subgroup of PwD who had mild or high deficits in the ADL and received the DCM showed a positive, however non-significant association. For PwD with high comorbidity a positive and statistically significant interaction effect (b=+13,007; SE=4,607) and for PwD with very high comorbidity, a positive but non-significant interaction effect (b=+2,338; SE=13,134) was found using the individual NMB at λ=40,000€. Thus, the analysis of the associations between different interaction terms and individual NMB with λ=40,000€, 80,000€, and 160,000€ confirmed the results based on linear modelling [90].

Discussion

Comorbidity and costs in dementia

Comorbidity in addition to dementia was highly prevalent. All PwD had at least one additional chronic condition. The distribution between a low, medium and high level of comorbidity displayed that three times more PwD had a high comorbidity compared to a low comorbidity. Our findings emphasize that comorbidity was associated with a substantial increase in health care resource use and consequently, healthcare costs from a public payer perspective in dementia, especially higher medical care costs due to higher utilization of medications and medical aids. Total costs of PwD with a high comorbidity were 14% and 47% lower as compared to PwD with a low or high comorbidity level, respectively, causing the observed u-

shaped curve of total costs. The U-shape relation with increasing comorbidity level is predominantly based on the high use of formal care in these comorbidity subgroups. The utilization and costs of formal care are not related to comorbidity. Thus, health care costs do not increase linearly as comorbidity increases. When several conditions in addition to one main disease, like dementia, are prevalent, it would be reasonable that the health care costs rise due to an increasing need for more treatment and care as well as an impeded management of several co-existing diseases (for example, if a PwD also has diabetes and has to inject insulin several times every day additionally to dementia treatment). However, health care costs cannot be calculated as the sum of the costs of separate diseases depending on the nature of the interactions among co-existing diseases [93, 94]. Thus, health care costs could either be greater or less than the sum of the costs of individual illnesses [95].

A few analyses evaluated the association between comorbidity and health resource utilization or health care costs for a dementia population. Fillit et al. [96] analyzed the relationship between comorbid conditions and health care utilization and costs for patients with AD and estimated total annual costs of 8,370 EUR. In our analysis, total costs from a payer's perspective valued from 7,536€ (SD: 10,718€) for the low comorbidity sample to 9,480€ (SD: 8,666€) for the very high comorbidity sample. Thus, the calculated costs in the study of Fillet et al. are very similar to our findings. However, the health care utilization was more frequent and costs higher with each additional level of comorbidity in this study. This is in contrast to our observed u-shaped relation between health care utilization and costs. Hill et al. described the relationship between comorbid conditions and costs for patients with Alzheimer`s disease (AD) and related dementias in a Medicare managed care organization and measured total costs for PwD of 9,217 EUR [97], which is congruent to the calculated costs of our very high comorbidity subgroup. In contrast, Bähler et al. estimated total health care costs of 7,141 EUR on average in an elderly community-dwelling population with comorbidity, which is comparable to the estimated total health care costs of our low comorbidity sample [27]. As in our study, health care resource use was for most categories (e.g. physician visits, medications, and medical aids) more frequent with each additional level of comorbidity. The co-occurrence of multiple diseases in an individual has been linked to poor outcomes including increased physician visits, longer length of in-hospital stays, and higher number of medications and medical aids as well as increasing needs for formal and informal care.

Reasons for the high health resource utilization and costs of PwD having a moderate or high comorbidity could be the high demand for health services and medical treatments due to

dementia as well as the challenges in the management of dementia and additional coexisting diseases. Obstacles in patient compliance, greater difficulties in treatment as well as barriers in organizing post-discharge care are important issues in dementia [96, 98]. Unique challenges occur in identifying and managing comorbidities of dementia patients [99]. Special efforts should be made to deal with existing comorbidities in patients with dementia. Improvements in the detection and treatment of comorbid diseases should improve outcomes for PwD [100]. Therefore, innovative approaches like collaborative DCM are needed to improve management of treatment and care in PwD and could result in reduced long term costs.

In the study of Leon et al. 1998 lower monthly cost was observed in a sample of Alzheimer's patients with 1 or 2 additional conditions (1,367€) compared to PwDs with none (1,465€) or 3 and more comorbidities (1,677€) [101]. Our analysis revealed a similar result. The lower health care utilization and total cost for the subgroup with high comorbidity compared to the subgroup with low comorbidity of the intervention group was one of the most surprising results in our analysis. We observed u-shaped health care costs in PwD with an increasing level of comorbidity as well. The results demonstrated that PwD appear to use in some cases fewer health care resources to treat comorbidity. This could maybe explain why in our high comorbidity subgroup the utilization of health care resources and health care costs are lower as in the low and very high comorbid subgroup. Our data shows a lower utilization of in-hospital days, rehabilitation days, and therapy visits in PwD with a high comorbidity compared to patients with low comorbidity and lower costs in these medical treatments.

Brillemann et al. (2013) revealed that there could be some cost-limiting comorbidities because treatment for the several conditions overlaps or because of inadequate care. In contrast, there can be comorbidities that increase costs compared with treating each condition separately [102]. In this study, some conditions were found to be both cost-increasing and some cost-limiting when co-occurring with other conditions except dementia, which was determined as a cost-limiting comorbidity. This finding is contrary to the evidence suggesting that PwD cause substantial higher cost as compared to non-demented controls of the same age [103-105]. However, the combination of different diseases in addition to dementia could increase or decrease cost, as demonstrated in the analysis of Brillmann. Besides, there is some evidence supporting that for PwD other conditions are under-reported or that the dementia diseases remains undiagnosed for a long time in the course of the diseases [106]. Underdiagnosis may also point to a lack of appropriate management of comorbidities [102, 107]. Thus, it could be assumed that in our high comorbidity sample the additional comorbidities in dementia are

combinations of cost-limiting comorbidities like diabetes, COPD, hypertension and chronic kidney disease [102]. This possibly indicates that treatment and care for PwD with these comorbidities are not as extensive as for those without dementia. In addition, it could be expected that in our low and very high comorbidity sample the additional comorbidities in dementia are combinations of cost-increasing comorbidities like depression and other mental diseases. However, the CCI does not consider psychological diseases. Depression was very common in our sample and identified in 15.4% of the PwDs but not considered in the CCI as a comorbid disease [56]. Further research is needed to evaluate if a consideration of mental illness would cause a more linear correlation between increasing cost and a higher comorbidity.

Subgroup cost-effectiveness analysis

Our second analysis of the cost-effectiveness of a collaborative DCM showed similar results when the different comorbidity groups were considered. PwD with a high comorbidity benefit more from a DCM as PwD having a low or very high comorbidity, represented by lower incremental costs and a higher probability of cost-effectiveness. Our multivariate analyses confirmed this significant association between the high comorbidity group of PwD and a higher NMBs. Thus, the longitudinal analysis, as well as the cross-sectional analysis, revealed comparable patterns, a "u-shape" of the individual cost-effectiveness for collaborative intervention and total healthcare costs over the comorbidity categories. It could be supposed that according to the lower total cost in PwD with a high comorbidity, the cost-effectiveness of the DCM is higher in the high comorbid sample as in the sample with low or very high comorbidities. It could be assumed that the higher the utilization of healthcare services, the higher would be the possibility to achieve cost-effectiveness of an intervention intending to optimize treatment and care by increasing the utilization of evidence- and high value-based treatment and care that could improve health and economic outcomes later on as well as would reducing the utilization of unnecessary and non-value based treatment and care that could end up in adverse patient- and economic-related outcomes. Contrary to this expectation, our findings suggest that solely for PwD with a high comorbidity but lower healthcare costs a high cost-effectiveness of the collaborative care program was achieved. For PwD with a low or very high comorbidity, the DCM is less cost-effective due to lower QALYs and higher costs. It can be assumed that the observed u-shape relation is caused by the high utilization and costs of formal care in theses comorbidity subgroups. PwD in the low and very high comorbidity subgroup utilize already at baseline a lot of formal care, so that the DCM may not have been so

effective and could not achieve as much as in patients with a low utilization of formal care (i.e. PwD with a high comorbidity).

Other studies indicated that individual comorbidities can be assigned to specific multimorbidity patterns and that the patterns influence and overlap with each other [22]. The combination of several comorbidities in addition to dementia could result in overuse, underuse, or misuse of health care services. Through the complexity and existing gaps between several sectors in the health care system, an individualized, comprehensive and coordinated care and treatment of all existing comorbidities did often not perform well in routine care. Our result that for PwD with a high comorbidity the DCM is more cost-effective than for PwD with a low or very high comorbidity indicated that a PwD with two or three comorbidities in addition to dementia has more unmet needs due to inappropriate and inadequate treatment in routine care. The DCM is a collaborative, integrated and comprehensive approach and therefore could detect and meet more needs across different diseases.

In addition to the presence of comorbidity in dementia, our work revealed that the age of the PwD, the degree of deficits in ADL, and the living situation of the patients (living alone) were significantly associated with higher health care costs in PwD. As shown in other studies, the age of the PwD is a key driver of health care costs and a higher comorbidity is associated with increasing age. [31] Furthermore, we found that more males than females with dementia have a high comorbidity burden. Differences in the diagnosis and treatment of comorbidity and health care service utilization in men and women might be some reasons. In the literature, there is some evidence that male PwD have a higher relative risk of comorbidity than women, compared with subjects without dementia, which is in accordance with our results [22, 108].

Additional findings

Our second analysis provides information about further patient subgroups, next to these PwD having a high comorbidity, that benefit more from a DCM. We found that female PwD who received the intervention shows significantly lower costs than do males due to significantly lower costs for in-hospital treatment and nursing home care. In addition, female people have higher net benefits than male patients. The positive net benefit for females implies that the value of the incremental benefit exceeded the incremental costs. The reasons could be the same as for alone living patients. Because female patients have more often no relatives or caregivers able to provide informal care needed to maintain living at home as long as possible. These PwD can benefit most from collaborative care management due to their higher number of unmet needs

that could be addressed in the DCM-intervention. In particular, arranging day and night care services as well as ambulatory care services could prevent unnecessary hospitalizations and delay the institutionalization, which both help saving healthcare costs.

Also, the DCM was more cost-effective in patients living alone, especially due to fewer physician visits and thereby significantly lower healthcare utilization and costs for treatment and care. Those patients benefit more from DCM because patients living alone have more unmet needs that a relative caregiver cannot take care of. Therefore, such patients receive more frequently professional care, reviewing the medication and assisting the PwD with taking the medication for example. However, further research is needed to clarify where professional care is more beneficial for patients than informal care.

Although, the previous cost-effectiveness analyses of DCM revealed that PwD living alone and receiving the DCM-intervention were less likely to be institutionalized, which incurs considerably lower nursing care costs [53]. The number of days stayed in the hospital was higher in the control group, especially for those living alone. Our results revealed that supporting PwD living alone could lead to reduced hospitalization. Therefore, patients living alone show higher net benefits due to higher positive effects when treating their individual unmet needs as part of the DCM-intervention.

Practical implications

Because dementia is not curable so far, improving treatment and care for both the dementia and al comorbidities according to evidence-based guidelines represents currently the best solution to satisfy PwD's and caregivers' needs. In addition, most PwD suffer from several additional comorbidities that are often un- or undertreated due to the prioritization in dementia treatment. In routine care, all necessary and required services and treatments for optimal guideline related treatment and care of dementia and comorbidities are available. However, the health-care system has become too complex so that PwD and their caregivers lack access to recommended guideline-based diagnosis, treatment, and care [109]. Therefore, there is a need for optimizing treatment and care of those being affected by dementia that interferes with caring for co-existing comorbidities. Collaborative, comprehensive, and managed care models for PwD like the DCM meet all these challenges and provide the affected patients with optimum support and evidence-based and guideline-based treatment by detecting all unmet needs and satisfy the open needs immediately in close cooperation between the service provider involved in treatment and care. However, the DCM is not equally beneficial for all PwDs. Regarding the level of comorbidity,

Pwd with a high comorbidity (two or three comorbidities in addition to dementia) could benefit most from the DCM intervention. Thus, these PwDs, as well as the health care system, could benefit considerably from DCM [53, 90]. Regarding the practical implications, our results recommend that at least for female and alone living PwDs, for PwD with a high comorbidity level and for PwD with mild and moderate cognitive deficits the DCM should be implemented into routine care immediately. For these subgroups of PwD the highest beneficial effects and substantial savings in costs could be achieved. In practice, the health insurances could screen their data and detect these PwD's and could offer the DCM to suitable insured patients. In addition, the physicians received additional reimbursement and billing options for these subgroups of patients. With these opportunities patients that benefit most from DCM could get adequate access to these collaborative dementia care model in ambulatory care.

In times of scarce resources, rising expenses for health care and increasing prevalence in dementia and other comorbidities, DCM could be one strategy to remedy this situation and could bring lasting relief for the health care system, for the healthcare payers as well for the health care providers. Especially GPs and specialists will not be capable to handle the increasing number of comorbid PwD adequately. Therefore, DCM programs could be a possible solution. PwDs with two or three additional comorbidities should be primarily addressed by a DCM. To provide adequate support for PwD with a high comorbidity, the present DCM could be extended or supplemented by programs for handling the most common and most cost-intensive comorbidities, for example, diabetes and vascular diseases (most common in combination with dementia) as well as cancer diseases, rheumatic disease or liver disease (most expensive in combination with dementia). Due to the typical cognitive decline in dementia disease, the patients often do not perceive the symptoms of their comorbidities or have difficulties to communicate them. Therefore, the needs of PwDs with comorbidities differ from PwD without comorbidities. Focusing on these comorbid subgroups can offer additional guidance on innovative and collaborative care models like the DCM and could improve the effectiveness of treatment, care, and service provision so that the needs of PwD are better met.

Limitations

The following limitations of the study have to be taken into consideration.

First, the DelpHi-trial was conducted in Mecklenburg Western Pomerania, a mostly rural area in north-eastern Germany. Access to the health care system could be weaker as compared to urban or suburban areas. Hence, the study area to some extent limits the generalizability of the

presented results. Second, we collected the healthcare resource use data via comprehensive standardized computer-assisted interviews and analyzed the information about utilization and costs retrospectively for one year. Therefore, there might be a recall-bias, that could lead to an underestimation of the utilization [110]. Thirdly, the results of our first analysis are based on cross-sectional baseline data. The majority of our sample was only mildly cognitively impaired PwD, which limits the generalizability of the presented results to more severely affected PwD.

In addition, we used the CCI to assess comorbidities in dementia. One particular shortage of the CCI is its negligence of psychiatric comorbidities, which are very common in PwDs. Nevertheless, the CCI is a validated and most commonly used index to measure comorbidity. Furthermore, the univariate analysis of costs showed lower costs for the high comorbidity group than for the low comorbidity group. One reason is that the patients of the low comorbidity group are limited to one comorbidity in addition to dementia. These additional conditions and combinations of comorbidities could be very different between the patients. This could lead to a bias in the results. Moreover, the number of patients between the intervention and control group was not equally balanced. Due to the impossibility to blind the intervention, patients in the control group withdrew their informed consents more frequently. However, there were no significant group differences regarding sociodemographic and clinical data at baseline.

Lastly, the net-benefit regression results depend on the maximum WTP per unit of effect. Caution should be exercised when normative statements are based on these values. We calculate a series of NMB values by using a huge range of cost-effectiveness ceiling ratios. The cost-effectiveness acceptability curve offers a convenient presentation of cost-effectiveness results for a range of threshold values of additional health benefits. However, the net-benefit framework has the same limitations as traditional cost-effectiveness analysis.

References

1. Harper, S., *Ageing societies*. 2014: Routledge.
2. Blüher, S. and A. Kuhlmey, *Demographischer Wandel, Altern und Gesundheit*, in *Soziologie von Gesundheit und Krankheit*. 2016, Springer. p. 313-324.
3. Becker, S., *Demografische Herausforderungen*, in *Pflege im Wandel gestalten – Eine Führungsaufgabe: Lösungsansätze, Strategien, Chancen*, P. Bechtel, I. Smerdka-Arhelger, and K. Lipp, Editors. 2017, Springer Berlin Heidelberg: Berlin, Heidelberg. p. 17-26.
4. Statistisches Bundesamt, *Bevölkerung Deutschlands bis 2060*, 2015: Wiesbaden.
5. Kuhn, B. and V.E. Amelung, *Gemeinden unter Druck–Welche Rolle kann die Kommune bei der Lösung von ambulanten ärztlichen Versorgungsproblemen spielen?* G&S Gesundheits-und Sozialpolitik, 2016. **69**(6): p. 16-24.
6. Gerlach, F., et al., *Bedarfsgerechte Versorgung-Perspektiven für ländliche Regionen und ausgewählte Leistungsbereiche.* Sachverständigenrat zur Begutachtung der Entwicklung im Gesundheitswesen, Gutachten, 2014.
7. Schulz, M., et al., *Zukünftige relative Beanspruchung von Vertragsärzten–Eine Projektion nach Fachgruppen für den Zeitraum 2020 bis 2035.* Versorgungsatlas-Bericht, 2016(16/02).
8. Rattay, P., et al., *Inanspruchnahme der ambulanten und stationären medizinischen Versorgung in Deutschland.* Bundesgesundheitsblatt-Gesundheitsforschung-Gesundheitsschutz, 2013. **56**(5-6): p. 832-844.
9. Peters, E., et al., *Demografischer Wandel und Krankheitshäufigkeiten.* Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz, 2010. **53**(5): p. 417-426.
10. Prince, M., et al., *World Alzheimer Report 2014-Dementia and Risk Reduction, an analysis of protective and modifiable risk factors*. 2014, London: Alzheimer´s Disease International (ADI).
11. Kricheldorff, C. and W. Hewer, *Versorgung von Menschen mit Demenz im gesellschaftlichen Wandel.* Zeitschrift für Gerontologie und Geriatrie, 2016. **49**(3): p. 179-180.
12. Wimo, A., et al., *The worldwide economic impact of dementia 2010.* Alzheimers Dement, 2013. **9**(1): p. 1-11.
13. Wimo, A., et al., *The worldwide costs of dementia 2015 and comparisons with 2010.* Alzheimer's & Dementia, 2017. **13**(1): p. 1-7.
14. Statistisches Bundesamt *Krankheitskosten*. https://www. destatis. de/DE/Publikationen/Thematisch/Gesundheit/Krankheitskosten/Krankheitskosten2120720089004. pdf?__blob=publicationFile, 2010.
15. Michalowsky, B., et al., *Medication cost of persons with dementia in primary care in Germany.* Journal of Alzheimer's Disease, 2014. **42**(3): p. 949-958.
16. Eichler, T., et al., *Living Alone with Dementia: Prevalence, Correlates and the Utilization of Health and Nursing Care Services.* Journal of Alzheimer's Disease, 2016. **52**(2): p. 619.
17. Förstl, H., *Demenzen: Perspektiven in Praxis und Forschung*. 2005: Elsevier, Urban & Fischer.
18. Bickel, H., *Demenzen im höheren Lebensalter: Schätzungen des Vorkommens und der Versorgungskosten.* Zeitschrift für Gerontologie und Geriatrie, 2001. **34**(2): p. 108-115.
19. Banerjee, S., *Multimorbidity—older adults need health care that can count past one.* The Lancet, 2015. **385**(9968): p. 587-589.

20. Bunn, F., et al., *Comorbidity and dementia: a scoping review of the literature.* BMC medicine, 2014. **12**(1): p. 192.
21. van den Akker, M., F. Buntinx, and J.A. Knottnerus, *Comorbidity or multimorbidity: what's in a name? A review of literature.* The European Journal of General Practice, 1996. **2**(2): p. 65-70.
22. van den Bussche, H., et al., *Which chronic diseases and disease combinations are specific to multimorbidity in the elderly? Results of a claims data based cross-sectional study in Germany.* BMC public health, 2011. **11**(1): p. 101.
23. Marengoni, A., et al., *Aging with multimorbidity: a systematic review of the literature.* Ageing research reviews, 2011. **10**(4): p. 430-439.
24. Vassilaki, M., et al., *Multimorbidity and risk of mild cognitive impairment.* Journal of the American Geriatrics Society, 2015. **63**(9): p. 1783-1790.
25. Dodel, R., *Multimorbidität: Konzept, Epidemiologie, Versorgung.* Der Nervenarzt, 2014. **85**(4): p. 401-408.
26. Browne, J., et al., *Association of comorbidity and health service usage among patients with dementia in the UK: a population-based study.* BMJ open, 2017. **7**(3): p. e012546.
27. Bähler, C., et al., *Multimorbidity, health care utilization and costs in an elderly community-dwelling population: a claims data based observational study.* BMC health services research, 2015. **15**(1): p. 23.
28. Mondor, L., et al., *Multimorbidity and healthcare utilization among home care clients with dementia in Ontario, Canada: A retrospective analysis of a population-based cohort.* PLoS medicine, 2017. **14**(3): p. e1002249.
29. Eckardt, M., et al., *Analysis of health care costs in elderly patients with multiple chronic conditions using a finite mixture of generalized linear models.* Health economics, 2017. **26**(5): p. 582-599.
30. Hager, K., et al., *Alzheimer-Demenz: Verlauf und Belastung der Pflegepersonen.* Der Nervenarzt, 2017.
31. Tonelli, M., et al., *Multimorbidity, dementia and health care in older people: a population-based cohort study.* CMAJ open, 2017. **5**(3): p. E623.
32. Savva, G.M. and B.C. Stephan, *Epidemiological Studies of the Effect of Stroke on Incident Dementia.* Stroke, 2010. **41**(1): p. e41-e46.
33. Whitmer, R.A., et al., *Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus.* Jama, 2009. **301**(15): p. 1565-1572.
34. Müller, B.S., et al., *Innovative Versorgungsmodelle in Deutschland–Erfolgsfaktoren, Barrieren und Übertragbarkeit.* Zeitschrift für Evidenz, Fortbildung und Qualität im Gesundheitswesen, 2016. **115**: p. 49-55.
35. Richter, S., *Integrierte Versorgung für Menschen mit Demenz.* Das Gesundheitswesen, 2015. **77**(11): p. 845-847.
36. Hoffmann, R., et al., *Delegation ärztlicher Leistungen.* Der Unfallchirurg, 2008. **111**(5): p. 367-370.
37. Thyrian, J.R., et al., *Effectiveness and Safety of Dementia Care Management in Primary Care: A Randomized Clinical Trial.* JAMA Psychiatry, 2017. **74**(10): p. 996-1004.
38. Dreier-Wolfgramm, A., et al., *Versorgungsmanagement bei Demenz in der Primärversorgung: Aktuelle kooperative Versorgungsmodelle und der Vorteil von interprofessionellem Lernen.* Zeitschrift fur Gerontologie und Geriatrie, 2017: p. 1-10.
39. Eichler, T., et al., *Dementia care management: going new ways in ambulant dementia care within a GP-based randomized controlled intervention trial.* International psychogeriatrics, 2014. **26**(2): p. 247-256.

40. Van den Berg, N., et al., *AGnES: Hausarztunterstützung durch qualifizierte Praxismitarbeiter.* Deutsches Ärzteblatt, 2009. **106**(1-2): p. 3-9.
41. Kalitzkus, V., I. Schluckebier, and S. Wilm, *AGnES, EVA, VerAH und Co–Wer kann den Hausarzt unterstützen und wie? Experten diskutieren die Zukunft der Medizinischen Fachangestellten in der hausärztlichen Versorgung.* Zeitschrift für Allgemeinmedizin, 2009. **85**: p. 403-405.
42. Reilly, S., et al., *Case management approaches to home support for people with dementia.* Cochrane Database Syst. Rev, 2015. **1**.
43. Callahan, C.M., et al., *Effectiveness of collaborative care for older adults with Alzheimer disease in primary care: a randomized controlled trial.* JAMA, 2006. **295**(18): p. 2148-2157.
44. Eloniemi-Sulkava, U., et al., *Effects of supporting community-living demented patients and their caregivers: a randomized trial.* Journal of the American Geriatrics Society, 2001. **49**(10): p. 1282-1287.
45. Vickrey, B.G., et al., *The effect of a disease management intervention on quality and outcomes of dementia care: a randomized, controlled trial.* Ann Intern Med, 2006. **145**(10): p. 713-726.
46. Miller, R., R. Newcomer, and P. Fox, *Effects of the Medicare Alzheimer's Disease Demonstration on nursing home entry.* Health Services Research, 1999. **34**(3): p. 691-714.
47. Newcomer, R., et al., *Effects of the Medicare Alzheimer's disease demonstration on Medicare expenditures.* Health Care Financing Review, 1999. **20**(4): p. 45-65.
48. Pimouguet, C., et al., *Dementia case management effectiveness on health care costs and resource utilization: a systematic review of randomized controlled trials.* The journal of nutrition, health & aging, 2010. **14**(8): p. 669-676.
49. Eichler, T., et al., *Unmet needs of community-dwelling primary care patients with dementia in Germany: Prevalence and correlates.* Journal of Alzheimer's Disease, 2016. **51**(3): p. 847-855.
50. Michalowsky, B., et al., *Healthcare utilization and costs in primary care patients with dementia: baseline results of the DelpHi-trial.* The European Journal of Health Economics, 2017: p. 1-16.
51. Thyrian, J.R., et al., *Life- and person-centred help in Mecklenburg-Western Pomerania, Germany (DelpHi): study protocol for a randomised controlled trial.* Trials, 2012. **13**: p. 56.
52. Dreier, A., et al., *Qualifications for nurses for the care of patients with dementia and support to their caregivers: A pilot evaluation of the dementia care management curriculum.* Nurse Educ Today, 2016. **36**: p. 310-7.
53. Michalowsky, B., et al., *Cost-effectiveness of Dementia Care Management Alongside a Cluster-Randomized Controlled Interventional DelpHi-Trial.* Alzheimers & Dementia 2019. **15**(10): p. 1296 - 1308.
54. Michalowsky, B., et al., *Economic Analysis of Formal Care, Informal Care, and Productivity Losses in Primary Care Patients who Screened Positive for Dementia in Germany.* J Alzheimers Dis, 2016. **50**(1): p. 47-59.
55. Thyrian, J.R., et al., *Systematic, early identification of dementia and dementia care management are highly appreciated by general physicians in primary care–results within a cluster-randomized-controlled trial (DelpHi).* Journal of multidisciplinary healthcare, 2016. **9**: p. 183.
56. Thyrian, J.R., et al., *Community-Dwelling People Screened Positive for Dementia in Primary Care: A Comprehensive, Multivariate Descriptive Analysis Using Data from the DelpHi-Study.* J Alzheimers Dis, 2016. **52**(2): p. 609-17.

57. Kaczynski, A., et al., *Comorbidity in Dementia Diseases and Associated Health Care Resources Utilization and Cost.* Journal of Alzheimer's Disease, 2019(Preprint): p. 1-12.
58. Powney, M., et al., *A review of the handling of missing longitudinal outcome data in clinical trials.* Trials, 2014. **15**: p. 237.
59. Faria, R., et al., *A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials.* Pharmacoeconomics, 2014. **32**(12): p. 1157-70.
60. Kessler, J., P. Denzler, and H. Markowitsch, *Mini-Mental-Status-Test (MMST). Deutsche Fassung.* Hogrefe Testzentrale, Göttingen, 1990.
61. Deuschl, G., Maier, W, Jessen, F, Spottke, A,, *S3-Leitlinie "Demenzen", Leitlinien für Diagnostik und Therapie in der Neurologie* Deutsche Gesellschaft für Neurologie (eds.), 2016.
62. Kessler, J., H.J. Markowitsch, and P. Denzler, *Mini-Mental-Status-Test (MMST) [German Version]*. 1990, Göttingen: Beltz Test GmbH.
63. Mackin, R.S., et al., *The sensitivity and specificity of cognitive screening instruments to detect cognitive impairment in older adults with severe psychiatric illness.* Journal of geriatric psychiatry and neurology, 2010. **23**(2): p. 94-99.
64. Kohn, N., et al., *Vergleich MMST und DemTect: Spezifität und Sensitivität bei primär kognitiven Störungen.* Akt Neurol, 2007. **34**(S 2): p. P672.
65. Hindmarch, I., et al., *The Bayer Activities of Daily Living Scale (B-ADL).* Dement Geriatr Cogn Disord, 1998. **9 Suppl 2**: p. 20-26.
66. Gauggel, S. and B. Birkner, *Validity and reliability of a German version of the Geriatric Depression Scale (GDS).* Zeitschrift fur Klinische Psychologie-Forschung und Praxis, 1999. **28**(1): p. 18-27.
67. Quan, H., et al., *Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data.* Medical care, 2005: p. 1130-1139.
68. Charlson, M.E., et al., *A new method of classifying prognostic comorbidity in longitudinal studies: development and validation.* Journal of chronic diseases, 1987. **40**(5): p. 373-383.
69. Bock, J.O., et al., *[Calculation of standardised unit costs from a societal perspective for health economic evaluation]*. Gesundheitswesen, 2015. **77**(1): p. 53-61.
70. Ware, J., M. Kosinski, and S.D. Keller, *A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity.* Med Care, 1996. **34**(3): p. 220-233.
71. Brazier, J.E. and J. Roberts, *The estimation of a preference-based measure of health from the SF-12.* Med Care, 2004. **42**(9): p. 851-859.
72. Billingham, L.J. and K.R. Abrams, *Simultaneous analysis of quality of life and survival data.* Stat. Methods Med Res, 2002. **11**(1): p. 25-48.
73. Billingham, L.J., K.R. Abrams, and D.R. Jones, *Methods for the analysis of quality-of-life and survival data in health technology assessment.* Health Technol Assess, 1999. **3**(10): p. 1-152.
74. Byford, S., D.J. Torgerson, and J. Raftery, *Economic note: cost of illness studies.* BMJ, 2000. **320**(7245): p. 1335.
75. Briggs, A.H. and A.M. Gray, *Handling uncertainty in economic evaluations of healthcare interventions.* BMJ, 1999. **319**(7210): p. 635-8.
76. Briggs, A.H., B.J. O'Brien, and G. Blackhouse, *Thinking outside the box: recent advances in the analysis and presentation of uncertainty in cost-effectiveness studies.* Annual review of public health, 2002. **23**(1): p. 377-401.
77. Hoch, J.S., M.A. Rockx, and A.D. Krahn, *Using the net benefit regression framework to construct cost-effectiveness acceptability curves: an example using data from a trial*

of external loop recorders versus Holter monitoring for ambulatory monitoring of" community acquired" syncope. BMC Health Services Research, 2006. **6**(1): p. 68.
78. Hoch, J.S., A.H. Briggs, and A.R. Willan, *Something old, something new, something borrowed, something blue: a framework for the marriage of health econometrics and cost-effectiveness analysis.* Health economics, 2002. **11**(5): p. 415-430.
79. Zethraeus, N., et al., *Advantages of using the net-benefit approach for analysing uncertainty in economic evaluation studies.* Pharmacoeconomics, 2003. **21**(1): p. 39-48.
80. De Ridder, A. and D. De Graeve, *Comparing the Cost Effectiveness of Risperidone and Olanzapine in the Treatment of Schizophrenia Using the Net-Benefit Regression Approach.* PharmacoEconomics, 2009. **27**(1): p. 69-80.
81. White, I.R., P. Royston, and A.M. Wood, *Multiple imputation using chained equations: Issues and guidance for practice.* Stat Med, 2011. **30**(4): p. 377-99.
82. Sterne, J.A., et al., *Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls.* BMJ, 2009. **338**: p. b2393.
83. Rubin, D.B. and N. Schenker, *Multiple imputation in health-care databases: an overview and some applications.* Stat Med, 1991. **10**(4): p. 585-98.
84. Desgagné, A., et al., *The use of the bootstrap statistical method for the pharmacoeconomic cost analysis of skewed data.* Pharmacoeconomics, 1998. **13**(5): p. 487-497.
85. World Health Organization (WHO), *The ICD-10 classification of mental and behavioural disorders: Diagnostic criteria for research.* 1993. **Volume 2**.
86. Obenchain, R.L., *Resampling and multiplicity in cost-effectiveness inference.* J Biopharm Stat, 1999. **9**(4): p. 563-82.
87. Neumann, P.J., J.T. Cohen, and M.C. Weinstein, *Updating cost-effectiveness--the curious resilience of the $50,000-per-QALY threshold.* N Engl J Med, 2014. **371**(9): p. 796-7.
88. Grosse, S.D., *Assessing cost-effectiveness in healthcare: history of the $50,000 per QALY threshold.* Expert Rev Pharmacoecon Outcomes Res, 2008. **8**(2): p. 165-78.
89. StataCorp, S., *Release 11.* Statistical Software College Station, TX: StataCorp LP, 2009.
90. Rädke, A., et al., *Who benefits most from collaborative dementia care from a patient and payer perspective? A subgroup cost-effectiveness analysis using the individual net monetary benefit approach.* Journal of Alzheimer's Disease, 2019. **(under review)**.
91. Vogeli, C., et al., *Multiple chronic conditions: prevalence, health consequences, and implications for quality, care management, and costs.* Journal of general internal medicine, 2007. **22**(3): p. 391-395.
92. Zulman, D.M., et al., *Quality of care for patients with multiple chronic conditions: the role of comorbidity interrelatedness.* Journal of general internal medicine, 2014. **29**(3): p. 529-537.
93. Charlson, M., et al., *Can disease management target patients most likely to generate high costs? The impact of comorbidity.* Journal of general internal medicine, 2007. **22**(4): p. 464-469.
94. Lehnert, T., et al., *Health care utilization and costs of elderly persons with multiple chronic conditions.* Medical care research and review, 2011. **68**(4): p. 387-420.
95. Valderas, J.M., et al., *Defining comorbidity: implications for understanding health and health services.* The Annals of Family Medicine, 2009. **7**(4): p. 357-363.
96. Fillit, H., J.W. Hill, and R. Futterman, *Health care utilization and costs of Alzheimer's disease: the role of comorbid conditions, disease stage, and pharmacotherapy.* FAMILY MEDICINE-KANSAS CITY-, 2002. **34**(7): p. 528-535.

97. Hill, J., et al., *Alzheimer's disease and related dementias increase costs of comorbidities in managed Medicare.* Neurology, 2002. **58**(1): p. 62-70.
98. Torian, L., et al., *The effect of dementia on acute care in a geriatric medical unit.* International Psychogeriatrics, 1992. **4**(2): p. 231-239.
99. Fox, C., et al., *The importance of detecting and managing comorbidities in people with dementia?* Age and ageing, 2014. **43**(6): p. 741-743.
100. Zekry, D., et al., *Demented versus non-demented very old inpatients: the same comorbidities but poorer functional and nutritional status.* Age and ageing, 2007. **37**(1): p. 83-89.
101. Leon, J., C.-K. Cheng, and P.J. Neumann, *Alzheimer's Disease Care: Costs And Potential Savings: Caring for persons with Alzheimer's disease in the community can save thousands of dollars, but at what cost to family caregivers?* Health Affairs, 1998. **17**(6): p. 206-216.
102. Brilleman, S.L., et al., *Implications of comorbidity for primary care costs in the UK: a retrospective observational study.* British Journal of General Practice, 2013. **63**(609): p. e274-e282.
103. Schwarzkopf, L., et al., *Excess costs of dementia disorders and the role of age and gender-an analysis of German health and long-term care insurance claims data.* BMC health services research, 2012. **12**(1): p. 165.
104. Michalowsky, B., A. Kaczynski, and W. Hoffmann, *Ökonomische und gesellschaftliche Herausforderungen der Demenz in Deutschland – Eine Metaanalyse.* Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz, 2019.
105. Leicht, H. and H.-H. König, *Krankheitskosten bei Demenz aus gesellschaftlicher Perspektive.* Bundesgesundheitsblatt-Gesundheitsforschung-Gesundheitsschutz, 2012. **55**(5): p. 677-684.
106. Eichler, T., J. Thyrian, and W. Hoffmann, *Rates of formal diagnosis in people screened positive for dementia in primary care and the effect of screning on diagnosis rates: Results of the Delphi-trial*, in *Alzheimer's & Dementia*2014. p. P610-P611.
107. Maslow, K. and E. Heck, *Dementia care and quality of life in assisted living and nursing homes: perspectives of the Alzheimer's Association.* The Gerontologist, 2005. **45**(suppl_1): p. 8-10.
108. Bauer, K., et al., *A claims data-based comparison of comorbidity in individuals with and without dementia.* BMC Geriatrics, 2014. **14**(1): p. 10.
109. Plsek, P.E. and T. Greenhalgh, *The challenge of complexity in health care.* BMJ, 2001. **323**(7313): p. 625-628.
110. Michalowsky B, F.S., Dreier A, Eichler T, Hertel J, König H, et al., *Healthcare utilization and total cost from payer and societal perspective in primary care patients with dementia – Baseline results of the DelpHi-trial.* European Journal of Health Economics, 2016.

Summary

Due to demographic changes, medical and nursing care in Germany faces new challenges. Combined with the aging of the population, an increase in age-associated diseases, including dementia, is to be expected. In addition to the increase in the number of persons with certain age-specific diseases, the aging of the German population also results in an increase in the number of persons with multiple diseases. The coexistence of dementia and comorbidity in people with dementia creates complex challenges for ambulatory and clinical care. The existence of comorbidity also leads to significantly higher medical costs.

Implementing new collaborative care programs and redistributing the responsibilities among outpatient care providers in the ambulatory care of patients may be one approach to ensure and improve the life and care situation of people with dementia. Collaborative Dementia Care Management, with the concept of support of general practitioners by specific qualified nurses demonstrated an adequate and effective approach for the compensation of supply deficits of PwD in the primary care sector. The aim of the dissertation is the health economic analysis of comorbidities in dementia and the evaluated Dementia Care Management of the DelpHi-MV study as an innovative approach for care and treatment of comorbidities in people with dementia. It is assumed that the cost of care for PwD varies depending on comorbidity and socio-demographic and clinical characteristics. Therefore, the health care costs of people with dementia are calculated and the association between these care costs and comorbidity and socio-demographic and clinical factors of PwD was analyzed. In addition, we aimed to detect important subgroups (e.g. PwD with low, high or very high comorbidity) who benefit most from the DCM intervention and for whom a significant effect on costs, Quality-adjusted Life Years (QALY) and on the individual cost-effectiveness could be achieved, considering different sociodemographic and clinical characteristics like comorbidity.

In the sample of PwD comorbidity was highly prevalent. 47% of PwD had a very high, 37% a high and only 16% a low comorbidity in addition to dementia. The most prevalent co-existing comorbidity were diabetes mellitus (42%), peripheral vascular disease (28%) and cerebrovascular disease (25%). Total costs significantly increased by 528 € (SE=214, CI 95%=109-947, p=0.014) with each further comorbidity, especially due to significantly higher cost for medication and medical aids. Compared with a low comorbidity, a very high comorbidity was significantly associated with 818 € (SE=168, CI 95%= 489-1147, p<0.001) higher medication costs and 336 € (SE=161, CI 95%=20-652, p=0.037) higher cost for medical aids. There was no significant association between a higher comorbidity and cost for formal

care services. The probability of DCM being cost-effective at a willingness-to-pay of 40,000€/QALY was higher especially in PwD having a high comorbidity (96% vs. 26% for patients with a low comorbidity), in females (96% vs. 16% for males), in those living alone (96% vs. 26% for those living not alone) and in those being moderately to severely cognitively (100% vs. 3% for patients without cognitive impairment) and functionally impaired (97% vs. 16% for patients without functional impairment).

Comorbidity in PwD represents a substantial financial burden on healthcare payer's and is a challenge for patients, healthcare providers and the health system. Innovative approaches are needed to achieve a patient-oriented management of treatment and care in comorbid PwD to reduce long-term costs. Collaborative dementia care management is one approach to solve these problems in dementia care. Thereby, patients characteristics significantly affect the cost-effectiveness of collaborative care. Female patients, patients living alone, and those with a high comorbidity as well as those being moderately cognitively and functionally impaired benefit most from DCM. For those subgroups of patients, healthcare payers could gain the highest cost savings and the highest effects on QALYs when the DCM approach will be implemented.

Appendix 1: Article Nr. 1 “Comorbidity in dementia diseases and associated health care resources utilization and cost

Journal of Alzheimer's Disease 68 (2019) 635–646
DOI 10.3233/JAD-180896
IOS Press

Comorbidity in Dementia Diseases and Associated Health Care Resources Utilization and Cost

Anika Kaczynski[a,*], Bernhard Michalowsky[a], Tilly Eichler[a], Jochen René Thyrian[a], Diana Wucherer[a], Ina Zwingmann[a] and Wolfgang Hoffmann[a,b]
[a]*German Center for Neurodegenerative Diseases (DZNE) site Rostock/Greifswald, Greifswald, Germany*
[b]*Institute for Community Medicine, Section Epidemiology of Health Care and Community Health, University Medicine Greifswald (UMG), Greifswald, Germany*

Handling Associate Editor: Sophie Vandepitte

Accepted 10 January 2019

Abstract.
Background: People with dementia (PwD) suffer from coexisting medical conditions, creating complex clinical challenges and increasing the risk of poor outcomes, which could be associated with high healthcare cost.
Objective: To describe the prevalence of comorbidity in PwD and to analyze the association between comorbidity in dementia diseases and healthcare costs from a payer's perspective.
Methods: This cross-sectional analysis was based on $n = 362$ PwD of the DelpHi-MV trial (Dementia: Life-and person-centered help in Mecklenburg-Western Pomerania). Comorbidity was assessed using the Charlson comorbidity index (CCI) and was categorized into low, high, and very high comorbidity. Healthcare resource utilization and unit costs were used to calculate costs. Multivariable regression models were applied to analyze the association between comorbidity and costs.
Results: Comorbidity was highly prevalent in the sample. 47% of PwD had a very high, 37% a high, and 16% a low comorbidity in addition to dementia. The most prevalent co-existing comorbidity were diabetes mellitus (42%), peripheral vascular disease (28%) and cerebrovascular disease (25%). Total costs significantly increased by 528€ ($SE = 214$, $CI_{95} = 109$–947, $p = 0.014$) with each further comorbidity, especially due to higher cost for medication and medical aids. Compared with a low comorbidity, a very high comorbidity was significantly associated with 818€ ($SE = 168$, $CI_{95} = 489$–1147, $p < 0.001$) higher medication costs and 336€ ($SE = 161$, $CI_{95} = 20$–652, $p = 0.037$) higher cost for medical aids. There were no significant association between a higher comorbidity and cost for formal care services.
Conclusions: Comorbidity in PwD represents a substantial financial burden on healthcare payers and is a challenge for patients, healthcare providers, and the health systems. Innovative approaches are needed to achieve a patient-oriented management of treatment and care in comorbid PwD to reduce long-term costs.

Keywords: Alzheimer's disease, comorbidity, dementia, economics, health care costs, health care resources

INTRODUCTION

Both medical and nursing health care, as well as the living conditions in older age that could be characterized by informal care given by family members, faces major challenges due to demographic changes. The

*Correspondence to: Anika Kaczynski, German Center for Neurodegenerative Diseases (DZNE), Ellernholzstraße 1-2, 17489, Greifswald, Germany. Tel.: +49 3834 86 75 07; E-mail: anika.kaczynski@dzne.de.

declining birth rate and the increasing life expectancy cause an aging of our society and an increase of age-associated illnesses, such as dementia [1, 2]. The prevalence of dementia is high. Between six and nine percent of the population over 65 years are currently suffering from dementia. According to a present estimate, there are about 50 million people living with dementia diseases worldwide [3, 4]. This number is expected to double every 20 years, reaching 132 million people with dementia (PwD) in 2050 [5]. In addition, dementia diseases are associated with a high utilization of health care resources and thus, health care costs were estimated to be 1 trillion US$ in 2018 worldwide [6, 7]. The increasing number of PwD and the associated high health care expenditures renders dementia diseases currently a health care priority [8–12].

Furthermore, the aging of the population causes an increase in the number of people having multiple diseases [13, 14]. Multimorbidity (the simultaneous existence of several diseases) or comorbidity (one or more other diseases in addition to the underlying disease) are very common, especially in elderly [15–17]. Comorbid patients are at a higher risk for dementia and other cognitive disorders [18]. The real prevalence of coexisting conditions is difficult to estimate due to the differences in conceptualization and age-related clustering. The numbers vary widely between the different studies, ranging from 3% to 62% [16, 19]. The over-60 s are estimated to have a prevalence ranging from 55% to 98% [18, 20]. Mondor et al. revealed that 89% of PwD had two or more coexisting diseases in addition to dementia [21]. The most common comorbidities in dementia are high blood pressure, osteoarthritis, hypercholesterolemia, diabetes mellitus, coronary artery disease, and depression [21–24].

The existence of different additional conditions in PwD creates complex challenges for health care providers, PwD, and their informal caregivers. Certain diseases, such as stroke and diabetes, may lead to faster cognitive decline [25, 26]. Dementia-related impairments often hinder a patient's ability to recognize concomitant diseases, comply with treatment regimens, or pass on the signs and symptoms of complications to health care providers. These limitations can lead to adverse results of treatment and care of PwD [14]. Furthermore, studies revealed that an increasing comorbidity in PwD was associated with a higher frequency of hospitalization [20, 23, 27–30]. Even though in the majority of studies comorbidity was shown to be a strong predictor for higher health care utilization rates and health care costs, especially in the elderly population, data are still scarce and inconsistent in terms of the impact of predisposing and influencing factors [31]. Knowledge of how coexisting comorbid conditions may affect the costs of dementia is rare. Notably, there is little known about the association between comorbidity and health care resource use as well as resulting health care cost in PwD [21, 23, 31, 32].

Aim of the Study

The objectives of this cross-sectional analysis were to determine the prevalence of comorbidity in community-dwelling PwD and to examine the association between comorbidity and health care costs.

MATERIALS AND METHODS

Study Design and Setting

This analysis was based on cross-sectional data of the DelpHi-MV trial (Dementia: life- and person-centered help in Mecklenburg-Western Pomerania), a pragmatic, general practitioner (GP)-based, cluster-randomized controlled prospective intervention trial [33, 34]. In this trial, Dementia Care Management was operationalized as a complex intervention aiming to provide optimal treatment and care for PwD and support to caregivers, provided by dementia-specific qualified nurses in close cooperation with the treating GP [33, 35, 36]. Initially, $n = 125$ GP practices participated, checked patients' eligibility criteria for the trial ($\geq$70 years, living at home), and screened for dementia using the DemTect, a widely used screening procedure [37, 38]. Patients who met the inclusion criteria (DemTect < 9) were informed by their GPs about the study, invited to participate, and asked to provide written informed consent. When patients were unable to provide written informed consent, their legal representative was asked to sign the consent form on their behalf. The study was approved by the local ethics committees and informed consent was obtained from caregivers and from patients (when possible) prior to inclusion. The design of the trial is described in detail in the study protocol [33].

Study Population

Overall, $n = 6{,}838$ people were screened by $n = 125$ GPs, yielding $n = 1.167$ (17%) PWD who were eligible for the study. Out of these, $n = 634$ (54%) gave an informed consent to participate in the DelpHi study. 118 PwD dropped out before starting the baseline assessment due to death ($n = 19$), withdrawal of informed consent ($n = 85$), relocation ($n = 5$), and other reasons ($n = 9$). In 154 patients, the dementia diagnosis (ICD-10: F00, F01, F02, F03, G30) could not be finally confirmed after the screening and before completing the baseline assessment. Hence, for the present analyses, data of $n = 362$ PwD with a confirmed diagnosis of dementia were used. The study flowchart is displayed in Supplementary Figure 1. To assess clinical and sociodemographic differences between the analyzed and excluded subsamples, a drop-out-analysis was conducted. The analysis shows that especially PwD with a higher DemTect Score dropped out probably due to lower cognitive impairments and absence of a final dementia diagnosis. In addition, many patients with a lower care level and thus with a lower need for care dropped out, as well as patients with a lower Charlson comorbidity index (CCI). The drop-out analyses are represented in the Supplementary Tables 1 and 2.

Sociodemographic and Clinical Factors

Sociodemographic variables (age, gender, living situation) and the following clinical variables were assessed: severity of cognitive impairment, number of medications, deficits in activities of daily living (ADL) and depression. Severity of cognitive impairment was assessed by the Mini-Mental Status Test (MMST) [39], a psychometric testing procedure to categorize participants into one of four groups of cognitive impairment: without ($\geq$27), mild (20–26), moderate (10–19), and severe ($\leq$9). The Bayer Activities of Daily Living Scale (B-ADL) [40] was used to assess deficits in ADL. Depression was assessed using the Geriatric Depression Scale (sum score 0–15, score $\geq$ 6 indicates depression) [41].

Diagnoses and Comorbidity

Medical diagnoses including the International Classification of Disease, 10th Revision (ICD-10) codes and the exact date of the initially received diagnosis, were retrieved from the patients' GP medical records. Comorbidity was identified by each patient's number of medical ICD-10 diagnoses listed in the GP's medical records. To provide a comorbidity summary score, an updated measure of the CCI by Quan was used, which is based on the ICD-10 System [42]. This measurement tool developed by Charlson et al. [43] is the most commonly used comorbidity score to measure the burden of disease or case-mix in health care data. The validated CCI considered in comparison to other comorbidity indexes the DRG-rules and distinguishes between the main and the secondary diagnosis. Through the absence and presence of different comorbid conditions, a weighted sum score could be derived. A higher score indicates a higher comorbidity. The weighted scores of the CCI relate to the existence of certain comorbidities as well as their severity levels in the evaluation. The following 17 different diseases were considered in the index: 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 [43]. Because all patients in our sample received a formal dementia diagnosis, we considered sixteen diseases for our analysis of comorbidity burden in addition to dementia.

The CCI use different weights for each of the 17 diseases (for details see Supplementary Table 3). A weighted sum score was calculated according to the recommendation of Quan [42]. Comorbidity was then categorized as follows: low (score = 1, one comorbidity in addition to dementia), high (score = 2–3, two or three comorbidities in addition to dementia) and very high comorbidity (score > 3, more than three comorbidities in addition to dementia). The calculation of the CCI as well as a description of ICD-10 Diagnoses included in each level of comorbidity is represented in Supplementary Formula 1 and Supplementary Table 3.

Health Care Utilization and Health Care Costs

The utilization of health care resources was retrospectively collected through comprehensive, standardized, computer-assisted interviews, assessing the utilization of healthcare services during the

Table 1
Methods and used unit costs for monetary valuation of medical and formal health care resources and services (based on Michalowsky et al. 2018 [54])

Cost categories	Services	Units	Unit costs†	Unit cost & source for monetary valuation
Medical care				
Out-patient physician treatment	GP or specialists	Contact	20.95€–81.56€, depending on specialization	Cost per contact [45]
In-patient treatment	In-hospital treatment and rehabilitation	Days	593.04€ and 121.85€, respectively	Average per diem cost for in-hospital treatment in Mecklenburg-Western Pomerania & for specialization of rehabilitation [45]
Medication	Prescribed drugs (Rx-drugs) in chronic use	Quantity	Market prices, 253.58€‡	Pharmaceutical Index of the Scientific Institute of the AOK [55]
Medical aids	Aids like tub-lift, tub-seats, walking sticks, walkers and others	Quantity	Market prices, 168.92€‡	Market prices
Other out-patient treatment	Occupational therapy, speech therapy, physiotherapy and others	Contacts	20.46€	Cost per contact & reimbursement schedules of statutory health insurance [56]
Formal care				
Ambulatory care	Home care provided by professionals	Quantity/ Contacts	Market prices, 11.48€‡	Market prices for Mecklenburg Western-Pomerania
Day care	Partial in-patient day- and night time nursing care and short-term care	Days	43.31€, 50.74€ and 57.94€, depending on care level*	Insurance rates of compulsory long-term in relation to patients level of care; including cost for board and lodging [57]
Nursing home care	Long-term care (institutionalization)	Days	61.17€, 76.36€ and 92.39€, depending on care level*	Insurance rates of compulsory long-term in relation to patients level of care; including cost for board and lodging [57]

GP, general practitioner; AOK, German public health insurance company; ADL, activities of daily living; IADL, instrumental activities of daily living; *care level one: mild functional impairment, care level two: moderate functional impairment, care level three: severe functional impairment; ‡when drugs, aids or services were unknown or market prices not available; †inflation included.

last 12 months. PwD, caregivers, and care services staff were interviewed face to face. For more precise information and to improve the validity of the data, the interviewer asked, if present, the participant's caregiver and staff of health care services as well. The records for health care utilization collected detailed information about the frequencies of the utilization of different medical (physician visits, medication, aids, in-hospital treatments, therapies) and formal care services (day and night care, ambulatory care, nursing home care). Details about the assessed medical and formal care services are displayed in Table 4.

Average costs per patient were calculated using the assessed healthcare resource utilization and published unit costs. Unit costs that were not available for the year 2018 were inflated by means of the recent years to 2018 values [44, 45]. The average inflation rate per year was for 2016 0.5%, for 2017 1.8%, and for 2018 1.9%. The used unit costs and methods for the monetary valuation of medical and formal health care resources and services are summarized in Table 1. Healthcare costs were calculated from a public payer's perspective, including all resources used that are completely attributable to the use of a healthcare intervention or illness (direct costs). These direct costs can be split into direct medical (physician visits, in-hospital treatments, medical aids, therapies) and non medical cost (day and night care, ambulatory care and nursing care). All these costs also include personnel and labor costs, administration, and other materials needed for specific treatments or care. In contrast, the payer perspective does not include indirect costs, for example patients' out-of-pocket spending or the costs of productivity losses due to illness. Total health care costs were defined as the sum of the medical care costs and costs of care. Informal care time of relative caregivers were not taken into account for this analysis.

Statistical Analysis

We used descriptive statistics to describe the sample characteristics and the prevalence of comorbidity. In order to be able to assess the statistical significance of group differences, Kruskal-Wallis test was performed. To analyze the associations between comorbidity and health care costs, we used multiple linear regression models with random effects for each GP (i.e., random-effects GLS regression). Cost for physician treatments, hospitalization, medication, medical aids, therapies, and formal care services as well as aggregated total costs were used as dependent variables in each model. The number of diseases according to CCI as well as the three levels of comorbidity were used as a predictor of interest in the models. We further used gender, age, living situation (dichotomous: living alone versus not alone), activities of daily living, and depression as covariates. Because of a highly skewed distribution of health care costs, standard errors and confidence intervals for regression coefficients were estimated by non-parametric bootstrapping with 2,000 replications. In addition, we conducted a sensitivity analysis to test the robustness of the results obtained by the multivariate linear regression, using a Generalized Linear Model (GLM) with a gamma distribution and log link. The results of the GLM are reported in Supplementary Table 5. Furthermore, a second sensitivity analysis using different categories for the severity of the comorbidity (linear mixed model with random effects) was performed. For this sensitivity analysis, a reclassification of the CCI with the following four comorbidity groups instead of three was used: 1) no comorbidities in addition to dementia (score = 1), 2) two comorbidities (score > = 2), 3) three or four comorbidities (score = 3–4) and 4) more than four comorbidities (score > 4) in addition to dementia. The results are reported in Supplementary Table 6. Statistical analyses were performed using the software STATA/IC Version 13.0 [46].

RESULTS

Sociodemographic and Clinical Characteristics

Patients were on average 81 ($SD = 5.5$) years old, mostly female (61.6%) and mildly cognitively and functionally impaired. The subgroup with a very high comorbidity was more likely to be male (49%, $n = 84$) compared to the subgroup with a low comorbidity (23%; $n = 13$; $p = 0.001$).

Of the $n = 362$ PwD, 37% ($n = 134$) showed a high and 47% ($n = 171$) a very high comorbidity according to the CCI.

Overall, the most prevalent comorbidities in addition to dementia were diabetes without chronic complication (42%), peripheral vascular disease (28%) and cerebrovascular disease (25%). The descriptive statistics of the characteristics of the total sample, as well as of the subgroups with a low, high, and very high comorbidity are shown in Table 2. The prevalences of the 17 identified diseases of the CCI as well as the costs per comorbidity in addition to dementia are displayed in Table 3.

Table 2
Relation of sociodemographic and clinical characteristics of the total sample with level of comorbidity ($n = 362$)

Variable	Level of comorbidity		
	Low comorbidity ($n = 57$)	High comorbidity ($n = 134$)	Very high comorbidity ($n = 171$)
Age			
Mean (SD)	81 (5.4)	81 (5.8)	80 (5.2)
Sex, n (%)			
Female	44 (77.2)	92 (68.7)	87 (50.9)
Number of medications			
Mean (SD)	5.3 (3.8)	6.7 (3.2)	8.3 (3.4)
MMSE			
Mean (SD)	21.8 (4.4)	21.7 (5.7)	21.4 (4.9)
Living situation, n (%)			
Alone	33 (57.9)	69 (51.5)	82 (47.9)
B-ADL			
Mean (SD)	4.2 (2.6)	3.8 (2.5)	4.2 (2.7)

[1] After screening (before screening rate was around 29%); 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; ICD, International Statistical Classification of Diseases and Related Health Problems, SD, standard deviation.

Table 3
Prevalence of comorbidities ($n = 362$) and costs per comorbidity in addition to dementia

Comorbidity[1]	Number	Percent (%)	Costs per comorbidity in dementia – mean (SD) in €
Dementia	362	100.0	–
Diabetes without chronic complication	153	42.3	7,877 (7,368)
Peripheral vascular disease	102	28.2	8,387 (9,095)
Cerebrovascular disease	92	25.4	8,136 (8,547)
Congestive heart failure	74	20.4	10,310 (8,521)
Chronic pulmonary disease	68	18.8	9,958 (10,089)
Renal disease	67	18.5	10,612 (8,850)
Diabetes with chronic complication	62	17.1	8,771 (7,836)
Any malignancy[2]	55	15.2	9,528 (8,960)
Mild liver disease	28	7.7	8,923 (10,765)
Acute myocardial infarction	15	4.1	6,106 (4,212)
Hemiplegia or paraplegia	15	4.1	9,588 (9,223)
Peptic ulcer disease	14	3.9	7,712 (9,047)
Rheumatic disease	12	3.3	11,348 (10,158)
Metastatic solid tumor	5	1.4	11,646 (6,900)
Moderate or severe liver disease	1	0.3	32,551 (0.0)
AIDS/HIV	0	0.0	0.0 (0.0)

[1]17 comorbidities based on the Charlson comorbidity index (CCI); [2]including lymphoma and leukemia, except malignant neoplasm of skin.

Health Care Utilization

Overall, the utilization of health care services was significantly higher in patients with a very high comorbidity compared to patients with a low comorbidity. PwD with a very high comorbidity were more frequently treated by physicians (mean visits 13 versus 11), were longer hospitalized (mean days stayed 5 versus 4 days), and took a higher number of medications (8 versus 4) compared to PwD with low comorbidity. In addition, the very high multimorbid sample utilized more formal care than the low multimorbid-sample (ambulatory care visits 167 versus 129; days of day/night care 13 versus 9). A detailed description of health care resource used for each level of comorbidity is represented in Table 4. All group differences were statistically significant, except the health cure days, day/night care and ambulatory care.

Health Care Costs

The mean costs for physician consultation (339€ versus 388€), the in-hospital costs (2,318€ versus 3.303€), the costs of medications (998€ versus 1.860€) as well as the costs for medical aids (663€ versus 948€) were higher in the sample with a very high comorbidity compared to the sample with low comorbidity. In contrast, the costs of therapy visits (e.g., occupational, physical, and speech therapy) were lower in the very high comorbidity group (101€) in comparison to the low comorbidity group (111€). In total, the annual medical care costs were higher in the very high comorbidity group (6,601€) compared to the low comorbidity group (4,431€). The costs for formal care were on average higher in the very high comorbidity group (2,879€) compared to the high comorbidity group (2,283€) but lower in comparison to the low comorbidity group (3,105€). Overall, mean total health care costs were highest in patients with a very high comorbidity compared to those with a low comorbidity (9,480€ for very high comorbidity, 6,450€ for high comorbidity, and 7,536€ for low comorbidity). All cost differences were statistically significant, except the day/night care as well as the ambulatory care (both formal care). Table 4 illustrates the total health care costs according to the level of comorbidity.

Associations Between Health Care Costs, CCI, and Level of Comorbidity

Total costs from a payer's perspective significantly increased by 528€ ($SE = 214$, $CI_{95} = 109–947$, $p = 0.014$) with each further diagnosis captured by the CCI. We observed a significant trend between comorbidity and medical care cost: A one-unit increase in the CCI was significantly associated with higher medical care costs of 455€ ($SE = 174$, $CI_{95} = 114–795$, $p = 0.009$). Compared with patients with a low comorbidity, a very high comorbidity was associated

Table 4
Health care resource utilization and costs by level of comorbidity ($n = 362$)

	Level of comorbidity			
	Low comorbidity ($n = 57$)	High comorbidity ($n = 134$)	Very high comorbidity ($n = 171$)	p^{**}
Health care resource use, mean (SD), median				
Medical treatments				
Physician, visits	10.8 (10.2), 10	11.7 (8.8), 10	12.7 (7.8), 12	0.022
In-hospital, days	3.7 (10.0), 0	2.4 (7.9), 0	5.1 (9.7), 0	0.003
Medication, number	4.2 (2.3), 4	5.8 (2.8), 6	7.5 (3.1), 7	0.001
Medical aids, number	3.6 (2.6), 3	4.6 (2.8), 4	5.4 (2.7), 5	0.001
Rehabilitation, days	0.4 (2.8), 0	0.0 (0.0), 0	1.0 (5.8), 0	0.032
Health cure, days	0.0 (0.0), 0	0.3 (2.2), 0	0.3 (2.5), 0	0.481
Therapies, visits	5.4 (13.1), 0	4.7 (16.5), 0	4.9 (13.7), 0	0.015
Formal care				
Day/ night care, days	8.6 (26.6), 0	7.8 (38.2), 0	13.4 (46.8), 0	0.070
Ambulatory care, visits	128.8 (277.3), 0	99.7 (262.4), 0	167.1 (336.5), 0	0.061
*Costs in Euros, mean (SD)**				
Medical treatments	**4,431 (7,113), 1,975**	**4,167 (5,531), 2,573**	**6,601 (6,724), 3,829**	**0.001**
Physicians	339 (455), 252	374 (374), 304	388 (243), 369	0.012
In-hospital	2,318 (6,308), 0	1,550 (4,867), 0	3,303 (6,227), 0	0.002
Medication	998 (1,037), 755	1,415 (1,365), 1,142	1,860 (1,462), 1522	0.001
Medical aids	663 (837), 491	733 (873), 491	948 (999), 722	0.001
Therapies	111 (268), 0	95 (338), 0	101 (280), 0	0.015
Formal care	**3,105 (5,280), 563**	**2,283 (4,874), 0**	**2,879 (5,231), 260**	**0.041**
Day/ night care	1,191 (2,605), 304	1,179 (3,337), 0	1,124 (2,929), 0	0.098
Ambulatory care	1,914 (4,474), 0	1,104 (2,894), 0	1,755 (3,501), 0	0.066
TOTAL COST (Payer perspective)	**7,536 (10,718), 2,786**	**6,450 (7,703), 3,446**	**9,480 (8,666), 6,412**	**0.001**

*Time period of costs: 12-month retrospective; demonstrated costs are annual mean costs per patient or patient group. **statistical significance of the difference between the low, high and very high comorbidity sample; Kruskal-Wallis were performed.

with 818€ ($SE = 168$, $CI_{95} = 489$–1147, $p < 0.001$) higher medication costs and with 336€ ($SE = 161$, $CI_{95} = 20$–652, $p = 0.037$) higher cost for medical aids. In contrast, there were no significant associations between a higher comorbidity and costs for physician consultations, in-hospital costs and therapy costs as well as for formal care cost. Tables 5 and 6 illustrate the association between the costs, the CCI, and the level of comorbidity. The GLM regression model with gamma distribution and log link confirmed a significant association between comorbidity and costs (Supplementary Table 5).

In contrast, the reclassified CCI with four severity groups (Supplementary Table 6) revealed no significant association between the total costs and each further diagnosis. However, the association between comorbidity and medication costs as well as with costs for medical aids were still significant.

DISCUSSION

We found a high burden of co-existing comorbid conditions in community-dwelling people with dementia. PwD had at least one additional chronic condition in addition to dementia. The distribution between a low, high, and very high comorbidity displayed that 84% of the PwD had at least a high comorbidity and three times more PwD had a very high comorbidity compared to a low comorbidity. Diabetes and vascular diseases represented the most common comorbidities in PwD. The prevalence of comorbidity observed in our sample is consistent with previously published studies [21, 23–26, 29, 30, 47].

Our findings emphasize that comorbidity is associated with a substantial increase of health care resource use and thus, costs in dementia. Utilization of more medications and medical aids characterized the community-dwelling PwD with very high comorbidity compared to PwD with low comorbidity. Therefore, PwD with a very high comorbidity caused higher total health care cost from a payer's perspective. In detail, predominantly the medical care costs (as one part of the total health care costs) are significantly associated with higher comorbidity rather than the costs of care.

There are only a few analyses evaluating the association between comorbidity and health resource utilization or health care costs in dementia. However, results of such analyses are comparable to the demonstrated results of this study. Hill et al. [30]

Table 5
Multivariable association between Charlson comorbidity index (CCI) and different cost categories ($n = 362$)

	Physicians[1] b (SE) [$CI_{95\%}$]	In-hospital cost[1] b (SE) [$CI_{95\%}$]	Medication[1] b (SE) [$CI_{95\%}$]	Medical aids[1] b (SE) [$CI_{95\%}$]	Out-patient therapies[1] b (SE) [$CI_{95\%}$]
Charlson comorbidity index[2]	4.88 (7.63) [–10.07–19.83]‡	266.48 (153.85) [–35.06–568.01]‡	118.65 (32.03) [55.88–181.42]***	64.30 (31.41) [2.73–125.86]*	3.34 (10.01) [–16.28–22.96]‡
Level of comorbidity (Ref. low comorbidity)[3]					
High comorbidity	51.81 (39.11) [–24.85–128.47]‡	–670.66 (930.69) [–2494.77–1153.45]‡	460.32 (127.70) [210.04–710.61]***	98.03 (130.83) [–158.39–354.44]‡	–8.37 (39.81) [–86.40–69.67]‡
Very high comorbidity	47.30 (49.23) [–49.18–143.78]‡	781.22 (977.00) [–1133.68–2696.11]‡	817.97 (167.98) [488.74–1147.20]***	336.20 (161.21) [20.22–652.17]*	–14.80 (44.02) [–101.10–71.48]‡

[1]Linear mixed model with random effects for general practitioner; standard errors were estimated with a nonparametric bootstrapping (2,000 replications); b, observed coefficient; SE, standard errors; model adjusted for age, gender, living situation (alone versus not alone), Geriatric Depression Scale score, Bayer activities of daily living score. [2]*Cost physicians, visits:* R^2 within = 0.024; R^2 between = 0.136; R^2 overall = 0.044; $p = 0.000$; *Costs in-hospital, days:* R^2 within = 0.071; R^2 between = 0.021; R^2 overall = 0.051; $p = 0.000$; *Costs medications, number:* R^2 within = 0.120; R^2 between = 0.089; R^2 overall = 0.121; $p = 0.000$; Cost medical aids: R^2 within = 0.104; R2 between = 0.145; R^2 overall = 0.132; $p = 0.000$; Costs out-patient therapies, visits: R^2 within = 0.113; R^2 between = 0.002; R^2 overall = 0.072; $p = 0.080$. [3]*Cost physicians, visits:* R^2 within = 0.027; R^2 between = 0.139; R^2 overall = 0.044; $p = 0.000$; *Costs in-hospital, days:* R^2 within = 0.065; R^2 between = 0.044; R^2 overall = 0.053; $p = 0.001$; *Costs medications, number:* R^2 within = 0.122; R^2 between = 0.152; R^2 overall = 0.124; $p = 0.000$; Costs medical aids: R^2 within = 0.093; R^2 between = 0.168; R^2 overall = 0.127; $p = 0.000$; Costs out-patient therapies, visits: R^2 within = 0.115; R^2 between = 0.001; R2 overall = 0.071; $p = 0.112$. ***0.001, **0.01, *0.05, ‡0.10.

Table 6
Multivariable association between Charlson comorbidity index (CCI) and total health care costs ($n = 362$)

	Costs for medical treatments[1] b (SE) [$CI_{95\%}$]	Costs for formal care services[1] b (SE) [$CI_{95\%}$]	Total costs[1] b (SE) [$CI_{95\%}$]
Charlson comorbidity index[2]	454.47 (173.66) [114.10–794.83]**	73.47 (109.76) [–141.66–288.59]‡	527.93 (213.74) [109.01–946.85]*
Level of comorbidity (Ref. low comorbidity)[3]			
High comorbidity	–89.28 (994.51) [–2038.48–1859.93]‡	–530.34 (659.90) [–1823.70–763.03]‡	–619.61 (1263.55) [–3096.12–1856.89]‡
Very high comorbidity	1942.97 (1099.05) [–211.13–4097.07]‡	–105.20 (697.58) [–1472.42–1262.02]‡	1837.77 (1378.17) [–863.40–4538.94]‡

[1]Linear mixed model with random effects for general practitioner; standard errors were estimated with a nonparametric bootstrapping (2,000 replications); b, observed coefficient; SE, standard errors; model adjusted for age, gender, living situation, Geriatric Depression Scale score, Bayer activities of daily living score. [2]*Costs for medical treatment:* R^2 within = 0.117; R^2 between = 0.059; R^2 overall = 0.091; $p = 0.000$; *Costs for formal care services, visits:* R^2 within = 0.256; R^2 between = 0.304; R^2 overall = 0.257; $p = 0.000$; *Total costs:* R^2 within = 0.194; R^2 between = 0.168; R^2 overall = 0.172; $p = 0.000$. [3]*Costs for medical treatment:* R^2 within = 0.109; R^2 between = 0.073; R^2 overall = 0.088; $p = 0.000$; *Costs for formal care services, visits:* R^2 within = 0.256; R^2 between = 0.320; R^2 overall = 0.258; $p = 0.000$; *Total costs:* R^2 within = 0.187; R^2 between = 0.201; R^2 overall = 0.169; $p = 0.000$. ***0.001, **0.01, *0.05, ‡0.10.

described the relationship between comorbid conditions and costs for patients with Alzheimer's disease (AD) and related dementias in a Medicare managed care organization and measured total costs for PwD of 9,217€ (10,723$; exchange rate 7/18/2018). Bähler et al. [32] estimated total health care costs of 7,141€ (8,301CHF; exchange rate 7/18/2018) on average in an elderly community-dwelling population with comorbidity. In addition, Fillit et al. [29] analyzed the relationship between comorbid conditions and health care utilization and costs for patients with AD and estimated total annual costs of 8,370€ (9,737$; exchange rate 7/18/2018). As in the current study, the health care utilization and costs were more frequent with each additional level of comorbidity. The co-occurrence of multiple diseases in an individual has been linked to poor outcomes including increased frequency of physician visits, longer length of in-hospital stays, and higher number of medications and medical aids as well as increasing needs for formal and informal care. The calculated costs in previous studies are similar to our findings [29, 30, 32].

The comorbidity (alone and independently from the main diagnosis) could be the main reason for the high health care utilization and costs. The increased

number of medications in PwD with very high comorbidity indicates that this health care resource use is associated with the variety of diseases and thus the comorbidity is not attributable to the dementia. In contrast, the high use of medical aids could be a result of dementia diseases. Progressive dementia goes along with increasing physical deficits. This may increase the need for medical aids in PwD.

Fillet et al. [29] showed that after controlling for comorbid conditions total annual costs were 3,268€ (3,8051$; exchange rate 7/18/2018) higher for patients with AD than for patients without AD. In addition, for the most prevalent comorbidities for AD patients, adjusted costs and utilization were higher for AD patients compared with None-AD-patients with the same condition. In a study by Schwarzkopf et al. [58] annual expenditures were approximately 12,300€ for patients with dementia and 4,000€ for non-demented control subjects. Thus, patients with dementia were approximately three times more expensive than non-demented control subjects [48]. In our study, mean total health care costs in PwD with a very high comorbidity were about 9,480€.

In addition to the presence of dementia disease as well as the comorbidity, this analysis revealed that the deficits in ADL, the age of the PwD and the living situation of the patients (living alone) was significantly associated with higher health care costs (see Supplementary Table 4). As shown in other studies, comorbidity increases with the age of the PwD and is a key driver of health care costs [24]. Furthermore, we found that more males than females with dementia have a very high comorbidity burden. Van den Bussche et al. [16] and Bauer et al. [48] reported that, compared with subjects without dementia, men with dementia have a higher relative risk of comorbidity than women with dementia. There might be differences in the diagnosis of comorbidity and health care service utilization in men and women. Overall, PwD living alone tended to be older and more often female [11]. We also hypothesize that male patients with dementia probably still live with a wife who is watchful about regular physician's visits and that older women are more likely to live alone without anyone caring for their health care needs. If this would be the truth, older women living with dementia are more likely to be underserved.

Other reasons for the high health resource utilization and costs of PwD having a high or very high comorbidity could be the challenges in the management of dementia and additional and coexisting diseases. Hurdles in patient compliance, greater difficulties in treatment adherence, a predisposition for infections as well as barriers in organizing post-discharge care are important issues [29, 49]. In addition, unique challenges occur in identifying and managing multimorbidities for dementia patients [50], for example, in communicating medical complaints because of deficits in the ability to speak. Special efforts should be made to deal with existing comorbidities in patients with dementia. Improvements in the detection and treatment of comorbid diseases should improve outcomes for people with dementia [51]. Studies have shown that patients with comorbidity are commonly underserved by poorly integrated care systems [52, 53]. Current evidence suggests that people with dementia did not have the same access to treatment and monitoring for conditions as those with similar comorbidities but without dementia [14]. Therefore, innovative approaches are needed to implement a better management of treatment and care in dementia diseases. This could reduce long-term costs. The fact that most of the elderly population suffer from multiple diseases should urgently be addressed by health care professionals as well as policymakers because the clinical needs differ from patients with only one disease. In terms of the expenses for health care systems, future health care costs cannot be calculated as the sum of the costs of single diseases [31]. Therefore, further research and studies on health care expenditures through dementia and various types of dementia (frontotemporal dementia, Parkinson's disease, etc.) and comorbidity are needed.

Limitation

Some limitations of the study have to be taken into consideration. Firstly, our findings are based on cross-sectional baseline data. The distribution of dementia severity within our sample is likely to change over a large number of follow-up visits after intervention. In baseline assessment, many patients only suffered from mild dementia. Future studies should analyze such changes. Secondly, the generalizability of the results might be limited due to the region under analysis. The access to the health care system could be different between rural and urban areas. Hence, the study area may have important implications on the health care utilization, for example with respect to ambulatory care use or to physician visits. The DelpHi-MV trial was conducted to test the efficacy of Dementia Care Management as an intervention. It was not specifically intended to test the association

between severity of comorbidity and health care costs. This renders the sample with respect to our *post-hoc* analysis of comorbidity and costs rather a convenience sample. Thirdly, the original CCI was developed to assess the 1-year mortality risk in patients with comorbidities. The prediction of survival or mortality over an ensuring year was not included in our analysis because this was not our research question. Fourth, the univariate analysis of costs shows lower costs for the high comorbidity group than for the low comorbidity group. One reason is that the patients of the low comorbidity group are limited to one comorbidity in addition to dementia. These additional conditions could be very different between the patients. This could lead to a bias in the results and thus, the "u-shape" of cost over the comorbidity categories. The sensitivity analysis confirmed the non-linear distribution of costs between the groups, but not as severe as in the initial analysis.

At last, we collected the healthcare resource use data via comprehensive standardized computer-assisted interviews and analyzed the information about formal costs and utilization retrospectively for a period of one year. There might be a recall-bias, that could lead to an under- or overestimation of the utilization. A prospective study or the use of secondary data or health insurance data could have avoided the recall bias but would have the disadvantage that the data are often not so comprehensive and can solely take into account formally diagnosed patients. As shown in other studies, only twenty to fifty percent of PwD receive a formal dementia diagnosis [12]. To reduce the recall bias in our study, the interviewer also asked the participant's caregiver and staff of health care services to validate the data. The in-person interviews were the most reasonable and appropriate method to collect the data in the given setting and within these sample, because all study participants were elderly, community-dwelling patients with dementia and their caregivers.

ACKNOWLEDGMENTS

This study is part of the DelpHi-MV trial (Dementia: Life- and person-centered help in Mecklenburg-Western Pomerania) and was funded by the German Center for Neurodegenerative Diseases (DZNE) and the University Medicine of Greifswald. Development, coordination and implementation of the DelpHi-MV study were influenced by input from several experts in their respective field and supported by an experienced field study team. Dr. Bernhard Michalowsky supported this analysis by teaching and supervising used methods.

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/18-0896r2).

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: http://dx.doi.org/10.3233/JAD-180896.

REFERENCES

[1] Blüher S, Kuhlmey A (2016) Demographischer Wandel, Altern und Gesundheit. In *Soziologie von Gesundheit und Krankheit* Springer, pp. 313-324.

[2] Peters E, Pritzkuleit R, Beske F, Katalinic A (2010) Demografischer Wandel und Krankheitshäufigkeiten. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* **53**, 417-426.

[3] World Health Organization (WHO), Dementia, http://www.who.int/mediacentre/factsheets/fs362/en/, Accessed 17 April 2018.

[4] World Health Organization (WHO), Towards a dementia plan: A WHO guide, http://apps.who.int/iris/bitstream/handle/10665/272642/9789241514132-eng.pdf?ua=1, Accessed 20. April 2018.

[5] Prince M, Comas-Herrera A, Knapp M, Guerchet M, Karagiannidou M (2016) *World Alzheimer report 2016: Improving healthcare for people living with dementia: Coverage, quality and costs now and in the future*. Alzheimer's Disease International, London, UK.

[6] Wimo A, Jonsson L, Bond J, Prince M, Winblad B (2013) The worldwide economic impact of dementia 2010. *Alzheimers Dement* **9**, 1-11.

[7] Wimo A, Guerchet M, Ali G-C, Wu Y-T, Prina AM, Winblad B, Jönsson L, Liu Z, Prince M (2017) The worldwide costs of dementia 2015 and comparisons with 2010. *Alzheimers Dement* **13**, 1-7.

[8] Förstl H (2005) *Demenzen: Perspektiven in Praxis und Forschung*, Elsevier, Urban & Fischer.

[9] Bickel H (2001) Demenzen im höheren Lebensalter: Schätzungen des Vorkommens und der Versorgungskosten. *Z Gerontol Geriatr* **34**, 108-115.

[10] Michalowsky B, Eichler T, Thyrian JR, Hertel J, Wucherer D, Laufs S, Fleßa S, Hoffmann W (2014) Medication cost of persons with dementia in primary care in Germany. *J Alzheimers Dis* **42**, 949-958.

[11] Eichler T, Hoffmann W, Hertel J, Richter S, Wucherer D, Michalowsky B, Dreier A, Thyrian JR (2016) Living alone with dementia: Prevalence, correlates and the utilization of health and nursing care services. *J Alzheimers Dis* **52**, 619.

[12] Eichler T, Thyrian JR, Hertel J, Köhler L, Wucherer D, Dreier A, Michalowsky B, Teipel S, Hoffmann W (2014) Rates of formal diagnosis in people screened positive for dementia in primary care: Results of the DelpHi-Trial. *J Alzheimers Dis* **42**, 451-458.

[13] Banerjee S (2015) Multimorbidity—older adults need health care that can count past one. *Lancet* **385**, 587-589.

[14] Bunn F, Burn A-M, Goodman C, Rait G, Norton S, Robinson L, Schoeman J, Brayne C (2014) Comorbidity and dementia: A scoping review of the literature. *BMC Med* **12**, 192.

[15] van den Akker M, Buntinx F, Knottnerus JA (1996) Comorbidity or multimorbidity: What's in a name? A review of literature. *Eur J Gen Pract* **2**, 65-70.

[16] van den Bussche H, Koller D, Kolonko T, Hansen H, Wegscheider K, Glaeske G, von Leitner E-C, Schäfer I, Schön G (2011) Which chronic diseases and disease combinations are specific to multimorbidity in the elderly? Results of a claims data based cross-sectional study in Germany. *BMC Public Health* **11**, 101.

[17] Valderas JM, Starfield B, Sibbald B, Salisbury C, Roland M (2009) Defining comorbidity: Implications for understanding health and health services. *Ann Fam Med* **7**, 357-363.

[18] Vassilaki M, Aakre JA, Cha RH, Kremers WK, St Sauver JL, Mielke MM, Geda YE, Machulda MM, Knopman DS, Petersen RC (2015) Multimorbidity and risk of mild cognitive impairment. *J Am Geriatr Soc* **63**, 1783-1790.

[19] Dodel R (2014) Multimorbidität: Konzept, epidemiologie, versorgung. *Der Nervenarzt* **85**, 401-408.

[20] Marengoni A, Angleman S, Melis R, Mangialasche F, Karp A, Garmen A, Meinow B, Fratiglioni L (2011) Aging with multimorbidity: A systematic review of the literature. *Ageing Res Rev* **10**, 430-439.

[21] Mondor L, Maxwell CJ, Hogan DB, Bronskill SE, Gruneir A, Lane NE, Wodchis WP (2017) Multimorbidity and healthcare utilization among home care clients with dementia in Ontario, Canada: A retrospective analysis of a population-based cohort. *PLoS Med* **14**, e1002249.

[22] Hager K, Henneges C, Schneider E, Lieb M, Kraemer S (2017) Alzheimer-demenz: Verlauf und belastung der pflegepersonen. *Der Nervenarzt* **89**, 431-442.

[23] Browne J, Edwards DA, Rhodes KM, Brimicombe DJ, Payne RA (2017) Association of comorbidity and health service usage among patients with dementia in the UK: A population-based study. *BMJ Open* **7**, e012546.

[24] Tonelli M, Wiebe N, Straus S, Fortin M, Guthrie B, James MT, Klarenbach SW, Tam-Tham H, Lewanczuk R, Manns BJ (2017) Multimorbidity, dementia and health care in older people: A population-based cohort study. *CMAJ Open* **5**, E623.

[25] Savva GM, Stephan BC (2010) Epidemiological studies of the effect of stroke on incident dementia. *Stroke* **41**, e41-e46.

[26] Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP, Selby JV (2009) Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. *JAMA* **301**, 1565-1572.

[27] Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B (2012) Epidemiology of multimorbidity and implications for health care, research, and medical education: A cross-sectional study. *Lancet* **380**, 37-43.

[28] Kuo RN, Lai M-S (2013) The influence of socio-economic status and multimorbidity patterns on healthcare costs: A six-year follow-up under a universal healthcare system. *Int J Equity Health* **12**, 69.

[29] Fillit H, Hill JW, Futterman R (2002) Health care utilization and costs of Alzheimer's disease: The role of comorbid conditions, disease stage, and pharmacotherapy. *Fam Med* **34**, 528-535.

[30] Hill J, Futterman R, Duttagupta S, Mastey V, Lloyd J, Fillit H (2002) Alzheimer's disease and related dementias increase costs of comorbidities in managed Medicare. *Neurology* **58**, 62-70.

[31] Lehnert T, Heider D, Leicht H, Heinrich S, Corrieri S, Luppa M, Riedel-Heller S, König H-H (2011) Health care utilization and costs of elderly persons with multiple chronic conditions. *Med Care Res Rev* **68**, 387-420.

[32] Bähler C, Huber CA, Brüngger B, Reich O (2015) Multimorbidity, health care utilization and costs in an elderly community-dwelling population: A claims data based observational study. *BMC Health Serv Res* **15**, 23.

[33] Thyrian JR, Fiss T, Dreier A, Bowing G, Angelow A, Lueke S, Teipel S, Flessa S, Grabe HJ, Freyberger HJ, Hoffmann W (2012) Life- and person-centred help in Mecklenburg-Western Pomerania, Germany (DelpHi): Study protocol for a randomised controlled trial. *Trials* **13**, 56.

[34] Thyrian J, Hertel J, Wucherer D, Eichler T, Michalowsky B, Dreier-Wolfgramm A, Zwingmann I, Kilimann I, Teipel S, Hoffmann W (2017) Effectiveness and safety of dementia care management in primary care. A randomized clinical trial. *JAMA Psychiatry* **74**, 996-1004.

[35] Eichler T, Thyrian JR, Dreier A, Wucherer D, Kohler L, Fiss T, Bowing G, Michalowsky B, Hoffmann W (2014) Dementia care management: Going new ways in ambulant dementia care within a GP-based randomized controlled intervention trial. *Int Psychogeriatr* **26**, 247-256.

[36] Dreier A, Thyrian JR, Eichler T, Hoffmann W (2016) Qualifications for nurses for the care of patients with dementia and support to their caregivers: A pilot evaluation of the dementia care management curriculum. *Nurse Educ Today* **36**, 310-317.

[37] Calabrese P, Kessler J (2000) Screening for cognitive impairment in dementia - the DemTect procedure. *Eur Neuropsychopharmacol* **10**, 369.

[38] Thyrian JR, Hoffmann W (2012) Dementia care and general physicians-a survey on prevalence, means, attitudes and recommendations. *Cent Eur J Public Health* **20**, 270.

[39] Kessler J, Denzler P, Markowitsch H (1990) *Mini-Mental-Status-Test (MMST). Deutsche Fassung*. Hogrefe Testzentrale, Göttingen.

[40] Hindmarch I, Lehfeld H, de Jongh P, Erzigkeit H (1998) The Bayer Activities of Daily Living Scale (B-ADL). *Dement Geriatr Cogn Disord* **9**(Suppl 2), 20-26.

[41] Gauggel S, Birkner B (1999) Validity and reliability of a German version of the Geriatric Depression Scale (GDS). *Z Klin Psychol Forsch Prax* **28**, 18-27.

[42] Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi J-C, Saunders LD, Beck CA, Feasby TE, Ghali WA (2005) Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* **43**, 1130-1139.

[43] Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis* **40**, 373-383.

[44] Byford S, Torgerson DJ, Raftery J (2000) Economic note: Cost of illness studies. *BMJ* **320**, 1335.

[45] Bock JO, Brettschneider C, Seidl H, Bowles D, Holle R, Greiner W, Konig HH (2015) [Calculation of standardised unit costs from a societal perspective for health economic evaluation]. *Gesundheitswesen* **77**, 53-61.

[46] StataCorp S (2009) Release 11. *Statistical Software.* StataCorp LP, College Station, TX.

[47] Poblador-Plou B, Calderón-Larrañaga A, Marta-Moreno J, Hancco-Saavedra J, Sicras-Mainar A, Soljak M, Prados-Torres A (2014) Comorbidity of dementia: A cross-sectional study of primary care older patients. *BMC Psychiatry* **14**, 84.

[48] Bauer K, Schwarzkopf L, Graessel E, Holle R (2014) A claims data-based comparison of comorbidity in individuals with and without dementia. *BMC Geriatrics* **14**, 10.

[49] Torian L, Davidson E, Fulop G, Sell L, Fillit H (1992) The effect of dementia on acute care in a geriatric medical unit. *Int Psychogeriatr* **4**, 231-239.

[50] Fox C, Smith T, Maidment I, Hebding J, Madzima T, Cheater F, Cross J, Poland F, White J, Young J (2014) The importance of detecting and managing comorbidities in people with dementia? *Age Ageing* **43**, 741-743.

[51] Zekry D, Herrmann FR, Grandjean R, Meynet M-P, Michel J-P, Gold G, Krause K-H (2007) Demented versus non-demented very old inpatients: The same comorbidities but poorer functional and nutritional status. *Age Ageing* **37**, 83-89.

[52] Vogeli C, Shields AE, Lee TA, Gibson TB, Marder WD, Weiss KB, Blumenthal D (2007) Multiple chronic conditions: Prevalence, health consequences, and implications for quality, care management, and costs. *J Gen Intern Med* **22**, 391-395.

[53] Zulman DM, Asch SM, Martins SB, Kerr EA, Hoffman BB, Goldstein MK (2014) Quality of care for patients with multiple chronic conditions: The role of comorbidity interrelatedness. *J Gen Intern Med* **29**, 529-537.

[54] Michalowsky B, Xie F, Kaczynski A, Hoffmann W (2018) CE3-Cost-effectiveness of dementia care management alongside a cluster-randomized controlled interventional DelpHi-Trial. *Value Health* **21**, S3.

[55] WIdO (Wissenschaftliches Institut der AOK), GKV-Arzneimittelindex, http://www.wido.de/amtl_atc-code.html, 16.09.2016, Accessed April 2018.

[56] WIdO (Wissenschaftliches Institut der AOK), Heilmittel-Einzelpreise in EURO nach Kassenart- Stand Mai 2014, http://www.kvwl.de/arzt/verordnung/hhm/heilmittel/heilmittelpreise.pdf, 5/2014, Accessed April 2018.

[57] Statistische Ämter des Bundes und der Länder, Pflegestatistik 2013 - Pflege im Rahmen der Pflegeversicherung. Deutschlandergebnisse, https://www.destatis.de/DE/Publikationen/Thematisch/Gesundheit/Pflege/PflegeDeutschlandergebnisse.html, 2015.

[58] Schwarzkopf L, Menn P, Leidl R, Wunder S, Mehlig H, Marx P, Graessel E, Holle R (2012) Excess costs of dementia disorders and the role of age and gender-an analysis of German health and long-term care insurance claims data. *BMC Health Services Research* **12**, 165.

Appendix 2: Article Nr. 2 “Who benefits most from collaborative dementia care from a patient and payer perspective - a subgroup cost-effectiveness analysis

Journal of Alzheimer's Disease 74 (2020) 449–462
DOI 10.3233/JAD-190578
IOS Press

Who Benefits Most from Collaborative Dementia Care from a Patient and Payer Perspective? A Subgroup Cost-Effectiveness Analysis

Anika Rädke[a,b,*], Bernhard Michalowsky[a,c,d], Jochen René Thyrian[a], Tilly Eichler[a], Feng Xie[c,d] and Wolfgang Hoffmann[a,b]
[a]*German Center for Neurodegenerative Diseases (DZNE) site Rostock/Greifswald, Greifswald, Germany*
[b]*Institute for Community Medicine, Section Epidemiology of Health Care and Community Health, University Medicine Greifswald (UMG), Greifswald, Germany*
[c]*Program for Health Economics and Outcome Measures (PHENOM), Hamilton, Canada*
[d]*Department of Health Research Methods, Evidence and Impact (formerly Clinical Epidemiology and Biostatistics), McMaster University, Hamilton, Canada*

Accepted 7 January 2020

Abstract.
Background: Dementia care management (DCM) aims to provide optimal treatment for people with dementia (PwD). Treatment and care needs are dependent on patients' sociodemographic and clinical characteristics and thus, economic outcomes could depend on such characteristics.
Objective: To detect important subgroups that benefit most from DCM and for which a significant effect on cost, QALY, and the individual cost-effectiveness could be achieved.
Methods: The analysis was based on 444 participants of the DelpHi-trial. For each subgroup, the probability of DCM being cost-effective was calculated and visualized using cost-effectiveness acceptability curves. The impact of DCM on individual costs and QALYs was assessed by using multivariate regression models with interaction terms.
Results: The probability of DCM being cost-effective at a willingness-to-pay of 40,000€/QALY was higher in females (96% versus 16% for males), in those living alone (96% versus 26% for those living not alone), in those being moderately to severely cognitively (100% versus 3% for patients without cognitive impairment) and functionally impaired (97% versus 16% for patients without functional impairment), and in PwD having a high comorbidity (96% versus 26% for patients with a low comorbidity). Multivariate analyses revealed that females (b = –10,873; SE = 4,775, $p = 0.023$) who received the intervention had significantly lower healthcare cost. DCM significantly improved QALY for PwD with mild and moderate cognitive (b = +0.232, SE = 0.105) and functional deficits (b = +0.200, SE = 0.095).
Conclusion: Patients characteristics significantly affect the cost-effectiveness. Females, patients living alone, patients with a high comorbidity, and those being moderately cognitively and functionally impaired benefit most from DCM. For those subgroups, healthcare payers could gain the highest cost savings and the highest effects on QALYs when DCM will be implemented.

Keywords: Alzheimer's disease, cost-effectiveness acceptability curve, cost-effectiveness analysis, dementia, economic evaluation, health care costs, individual cost-effectiveness ratio, net benefit regression, net monetary benefit

*Correspondence to: Anika Rädke, German Center for Neurodegenerative Diseases (DZNE), Ellernholzstraße, 1-2, 17489, Greifswald, Germany. Tel.: +49 3834 86 75 07; E-mail: anika.raedke@dzne.de.

INTRODUCTION

At present, about 1.7 million people are estimated to live with dementia in Germany [1, 2]. Even though some latest evidence suggests a decline in age-specific incidences [3], prevalence of dementia is expected to double every 20 years due to an increase in life expectancy and a growing number of older people [4]. Dementia diseases represent one of the economically most important disease groups of older age [5, 6]. Without a cure, the focus of therapy and health care shifts to providing the best possible care.

According to variations in individual unmet needs and priorities of people with dementia (PwD), it is necessary to initiate and coordinate individualized patient-centered treatment and care that aimed to improve patients and caregivers outcomes and reduce health care cost for public payers [7]. This highlights the urgent need to incorporate the patient, (informal) caregiver, and other service providers in advanced care planning. Treatment and care needs are dependent on patients' sociodemographic and clinical characteristics and thus, economic outcomes could depend on such characteristics. To address all these demands, interdisciplinary and individualized treatment and care are crucial.

Collaborative care programs have proven their potential to achieve this. Care and case management interventions are based on evidence-based guidelines and recommendations, are usually delivered in the community, aim to detect existing unmet needs, and enhance the coordination of treatment and care within the primary health care system [8]. There is some evidence that collaborative care and case management approaches are beneficial by improving person-centered outcomes in PwD. The systematic review of Reilly et al. [8] demonstrated that case management programs could reduce hospitalizations and the length of hospital stays, may postpone institutionalization, alleviate behavior disturbance and depression, and improve social support for patients and caregivers. In Germany, there is scientific evidence for the efficacy and safety of a collaborative care program as well. In a general practitioner (GP)-based cluster-randomized controlled trial with $n = 634$ patients, it was demonstrated that people who benefited from Dementia Care Management (DCM) showed better dementia-specific treatment, higher prescription rate of anti-dementia drugs, less neuropsychiatric symptoms, and higher Health-related quality of life (HRQoL). Furthermore, caregivers burdened was reduced [9, 10].

Only a few studies evaluated the cost-effectiveness of such programs, revealing inconclusive evidence [8, 11–15]. This has been acknowledged by the World Alzheimer Report 2016, highlighting the need for economic evaluations. Even though the Cochrane review [8] pointed out that case management increases the use of community services, it is more cautious about the economic impact by stating that overall healthcare costs "may be" reduced in the first year. Other published studies on case management and support programs in PwD reported a reduction in quality-adjusted life years (QALY), but still a non-significant reduction in cost, which would be an inadequate scenario [16, 17].

Michalowsky et al. [7] determined the incremental cost-effectiveness ratio (ICER) of the collaborative dementia care management versus usual care in Germany and confirmed a significant gain in QALYs by modestly reducing health care cost over a 24 months' time horizon. However, savings in costs were rather uncertain.

The lack of significance may be due to lack of power for a cost effect as costs are highly skewed. It may also be due to an application of the program to individuals less likely to achieve improved health outcomes, reduced costs, or both. However, there is a lack of cost-effectiveness studies acknowledging the heterogeneous group of patients (for example, in sociodemographic or clinical parameters). Trial-based cost-effectiveness analyses typically adopt a cohort-based approach and compare the cost and effects of the intervention versus the control group using the entire trial sample. The individual effect of an intervention on the patient may be associated with certain individual sociodemographic and clinical characteristics of the patient, and its cost-effectiveness could therefore vary between subgroups. An individual cost-effectiveness analysis under consideration of different covariates could detect important subgroups where the effectiveness of such an intervention is higher from a health economic point of view.

Therefore, this study aimed to identify important sociodemographic and clinical characteristics of PwD receiving DCM that are associated with higher cost-effectiveness of the intervention.

MATERIALS AND METHODS

Study design

This analysis was based on longitudinal 24-months data of the DelpHi-MV trial, a pragmatic, GP-based,

cluster-randomized controlled prospective intervention trial, evaluating a collaborative DCM [9, 10]. The DCM of the DelpHi-MV study was developed to support PwD and their caregivers in primary care [9, 18]. The DCM was operationalized as a complex intervention aiming to provide optimal treatment and care for PwD and support to caregivers in close cooperation with the treating GP. It was provided by dementia-specific qualified nurses and supported by a computerized Intervention Management System [19, 20].

In total, 136 GP practices participated in this trial. Based on simple randomization without stratification or matching (1:1), these practices were randomized to the intervention (DCM) or to the control group (usual care). GP practices checked patients' eligibility for the trial ($\geq$70 years, living at home) and screened for dementia using the DemTect procedure [21]. PwD of a GP whose practice was randomized to the intervention group received the DCM; PwD of control group GPs received care as usual. The study protocol and documents for written informed consent were approved by the Ethical Committee of the Chamber of Physicians of Mecklenburg-Western Pomerania (registry number BB 20/11). The design of the trial is described in the study protocol [9, 10].

Sample

Initially, 6,838 people were screened at 128 GP practices, and $n = 1{,}167$ (17%) PWD were found eligible for the study. 634 PwD gave an informed consent to participate in this study and $n = 516$ started the baseline assessment (intervention: 348 PwD; controls: 168 PwD). A detailed description of this sample is given elsewhere [22]. After completing the baseline assessment, $n = 85$ participants withdrew their informed consent, $n = 73$ passed away, and $n = 6$ postponed the first and second follow-ups, resulting in a sample of 408 and 352 participants who accomplished the first and second follow-up. This analysis was conducted on a sample of 444 participants who received either the DCM or usual care and completed the baseline and at least one of the two follow-up assessments or died (dead patients were included in this analysis) [23, 24]. The study flow chart and the drop-out analyses are described in more detail elsewhere [7, 25].

Intervention

The intervention was developed according to current guidelines [26–29], targeted at the individual participant level, delivered at participants' homes by nurses with dementia-specific qualification, and focused on the management of interprofessional treatment and care, medication management and caregiver support and education. A specifically qualified nurse, the so-called Dementia Care Manager, collected data on medical, nursing, and social characteristics of each PwD and his or her caregiver [19]. The care managers subsequently identified patients' and caregivers' unmet needs. These needs were discussed, consented, and carried out in cooperation with the treating GP. The duration of the intervention was six months. The intervention is described in more detail by Eichler et al. [18]. Costs for implementing the DCM are presented by Michalowsky et al. [7]. Effectiveness, efficiency, and health economics of the DCM concept were published elsewhere [25, 30, 31].

Data assessment

Comprehensive data assessments were conducted at baseline, and after 12 and 24 months of follow-up. Baseline assessment, intervention, and annual follow-ups were carried out by dementia care managers.

HRQoL was measured using the 12-Item Short-Form Health Survey (SF-12), a generic, multidimensional instrument that measures the physical dimension of HRQoL with respect to the perception of general health, physical functioning, bodily pain, and role limitations due to the physical health state, as well as mental dimensions including social functioning, mental health, and vitality and role limitations due to emotional state [32].

Healthcare resource utilization was assessed retrospectively through face-to-face interviews. Within the standardized interviews with the PwD and their caregivers (as well as, if possible, with the professional care staff), a list of widespread healthcare resources and services were used. The utilization review assesses medical care services uses, such as physician visits, in-hospital treatments, medications, medical aids and therapies, ambulatory care, day care, and nursing home care.

Sociodemographic data included age, gender, and living situation (alone versus not alone). In addition, the following clinical variables were assessed: cognitive impairment (Mini-Mental State Examination, MMSE) [33], comorbidity (Charlson Comorbidity Index, CCI) using ICD-10 diagnoses listed in the patients GP files [34], depression (Geriatric Depres-

sion Scale, GDS) [35], and deficits in daily living activities (Bayer Activities of Daily Living Scale, B-ADL) [36].

Missing values were handled by Multiple Imputation by Chained Equations (MICE). Multiple imputation models were specified for each variable and adjusted for age, gender, living situation, and comorbidity [24, 37, 38]. Imputations were conducted on the item level, adding 50 additional data sets for each missing variable [7, 39].

Calculation of QALYs and costs

Health utilities were derived from the SF-12 using the method of Brazier & Roberts and used to calculate QALYs for each patient separately [40]. The responses to the SF-12 were converted to health utilities using the SF-6D algorithm. A linear change of HRQoL between baseline, 12 months, and 24 months was assumed, which is consistent with the nature of dementia diseases, represented by growing cognitive and functional deficits, in turn, increasingly affecting HRQoL. In addition, a linear relationship for the change of HRQoL has been found to be the most commonly used approach in the trial-based CEA literature and has been applied in other recent economic evaluations targeting PwDs [41–44]. In case of death (the exact date was recorded), the utility value was assumed to equal zero. Finally, individual QALYs were calculated by using the area under the curve technique and discounted at 5% per year [41, 42].

Published unit costs were used to calculate the average costs per patient. All costs were discounted at 5% per year and were calculated from a public payer's perspective in 2018 Euros over the two-year follow-up trial period [45, 46].

Definition of subgroups

Previous analyses revealed that, for example, patients living situation, comorbidity, or functional impairment were associated with higher costs or lower quality of life [7, 47, 48]. Therefore, specific patient subgroups of this analysis were derived from the following sociodemographic and clinical variables: sociodemographic characteristics considered were age (<80 years versus 80 years and older), sex (male versus female), and living arrangements (living alone versus not living alone); clinical characteristics considered were degree of comorbidity based on CCI (low (<2), high (2-3), and very high (>3)) [34], severity of cognitive impairment based on MMSE Score (none (>26), mild (20–26), and moderate to severe (0–19)) [29, 33], and deficits in daily living activities based on the B-ADL (no deficit (1.0–2.0), mild deficits (2.1–5.0), and high deficits (5.1–10.0) [36]).

Subgroup cost-effectiveness analysis

For each subgroup cost-effectiveness analysis, the complete sample has been split to generate consistent and homogeneous subgroups according to the mentioned sociodemographic and clinical variables listed above. Within each split sample, a full cost-effectiveness analysis was conducted, assessing the cost-effectiveness of the DCM compared to the control group as follows: The incremental cost-effectiveness ratio (ICER) was calculated using the incremental cost per QALY gained by the DCM program compared with usual care [49]. Due to the dependency of patients to clusters (GP practices), incremental costs and QALYs were estimated using linear regression models with random effects for the GP [41, 50, 51]. Because of a highly skewed distribution of cost, standard errors and confidence intervals were estimated by bootstrapping (2,000 replications) [52]. To handle sampling uncertainty in the ICER, we used non-parametric bootstrapping, creating 1,000 resamples [53]. The probability of the DCM being cost-effective was calculated using these resamples and different willingness-to-pay (WTP) margins and displayed using cost-effectiveness acceptability curves [54, 55]. The methods used for this analysis were consistent with those of published methodological guidelines for undertaking economic evaluations [56]. All statistical analyses were performed using the software STATA/IC Version 13.0 [57].

Sensitivity analysis: Implementing interaction terms to analyze the association between the individual cost-effectiveness and patient's characteristics

We assessed the impact of the DCM on individual total costs, QALY, and individual cost-effectiveness by using multivariate linear regression models with random effects as well. Total healthcare cost, QALYs, and the individual net monetary benefit (NMB), as a measure for the cost-effectiveness, was used as dependent variables. The individual NMB was assessed according to the recommendation of Ridder et al. [58–60]: each subject's NMB_i was defined

as follows, using the observed data on the effects (e_i) and cost (c_i) for a PwD (i):

$$NMB_i = e_i \cdot \lambda - c_i \quad (1)$$

The individual NMB approach requires a selection of a willingness-to-pay margin (λ). Due to the subjective nature of which ceiling ratio was used, we selected a threshold of 40,000€, 80,000€, and 160,000€per individual QALY (see Supplementary Table 1) [59].

To explore if the cost-effectiveness varies by subgroups, we used the following binary operators to specify factorial interactions between the subject characteristics and the intervention indicator as variables of interest: Study group (intervention) with age (reference:>80 years), sex (reference: female), living situation (reference: living alone), deficits in daily living activities (B-ADL) (reference: no deficits), cognitive deficits (MMSE) (reference: no indication for cognitive deficits), and comorbidity (CCI category) (reference: low comorbidity). Dummy variables were used as factor-variable operators for the categorical sociodemographic and clinical characteristics. The interaction terms with the intervention group were used to control for homogeneous effects across the single patient groups and to assign the mean cost, QALYs and individual NMB for different patient groups [61]. The interaction terms were additionally included as model variable. Each model was additionally adjusted for sociodemographic and clinical variables that were not included in the interaction term. Because of the highly skewed distribution of healthcare costs, standard errors and confidence intervals were again estimated by bootstrapping (2,000 replications) [62]. A description of the used STATA code, as well as visualization or the residuals of the linear regression models, are presented in Supplementary Document 1.

RESULTS

Characteristics of the study population

Patients were on average 80 years old, mostly female (60%), on average mildly cognitively (mean MMSE 22) and functionally impaired (mean B-ADL 4), and half of them were living alone (51%). 39% of the patients had a very high comorbidity (more than three comorbidities in addition to dementia). Table 1 describes the characteristics of the study population divided into intervention and control group. There were no significant differences in sociodemographic and clinical characteristics between intervention and controls. Subgroup sizes were as well balanced in the intervention and the control group.

Incremental cost, QALYs, and ICERs overall and for subgroups

Overall, PwDs receiving the DCM tended to incur lower cost of 569€(95% CI: –5,466€– 4,328€) and gained on average 0.05 (95% CI: –0.04 – 0.14) more QALYs compared to care as usual over the 24 months' time horizon. Therefore, DCM dominated the usual care.

For subgroups, features associated with the most promising ICERs were female and alone living, mild deficits in daily living, moderate to severe cognitive deficits, and a high comorbidity.

For females (–4,307 €and +0.04 QALY), and PwD living alone (–3,642 €and +0.03 QALY) as well as for PwD with mild functional (–2,678 €and +0.05 QALY) or moderate to severe cognitive deficits (–5,574 €and 0.10 QALY) and for PwD having a high comorbidity (–7,416 €and +0.07 QALY), the incremental cost was lower and the incremental QALYs was higher as compared to the entire sample, indicating a stronger dominance of the intervention. A description of the incremental cost and QALYs of the subgroups is presented in Table 2 and Supplementary Figure 1.

Probability of cost-effectiveness

The probability of cost-effectiveness for the total sample valued 88% at a WTP threshold of 40,000€per QALY gained. For old PwD (≥80 years) the probability of the DCM being cost-effective (i.e., had a higher NMB relative to control) was much higher compared to the young PwD (<80 years) at the WTP of 0€and 40,000€per QALY gained (65% versus 39% and 87% versus 48%, respectively). It can be observed that the probability that the intervention is cost-effective was very high in females compared to males at the WTP of 0€and 40,000€per QALY gained (86% versus 2% and 96% versus 16%, respectively). In addition, compared to PwD not living alone, the probability of cost-effectiveness was much higher in PwD living alone at WTP thresholds of 0€per QALY and 40,000€(82% versus 13% and 96% versus 26%, respectively).

Table 1
Subject characteristics by treatment group ($n = 444$)

	Intervention ($n = 315$)	Control ($n = 129$)	p
Age, n (%)			
young (<80 y)	177 (56.2)	67 (51.9)	0.572
old (≥80 y)	138 (43.8)	62 (48.1)	
Sex, n (%)			
Female	190 (60.3)	77 (59.7)	0.503
Male	125 (39.7)	52 (40.3)	
Living situation, n (%)			
Living alone	163 (51.8)	61 (47.3)	0.453
Living not alone	152 (48.3)	68 (52.7)	
Deficits in Daily Living Activities (B-ADL), n (%)			
no	107 (34.0)	51 (39.5)	0.112
mild	110 (35.0)	48 (37.2)	
high	92 (29.2)	29 (22.5)	
Cognitive Deficits (MMSE), n (%)			
no indication*	71 (22.5)	28 (21.7)	0.576
mild	159 (50.5)	68 (52.7)	
moderate to severe	85 (27.0)	33 (25.6)	
Comorbidity (Charlson Index), n (%)			
low	64 (20.3)	38 (29.4)	0.113
high	123 (39.0)	48 (37.2)	
very high	128 (40.6)	43 (33.3)	

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. *The MMSE is less sensitive for detecting milder forms of cognitive impairment (43%) compared to the DemTect procedure (80% to 100%) that was used for the screening in GP practices and the subsequent inclusion of patients in the trial [75, 76]. Therefore, it is possible that some patients, who were screened positive for dementia, are not cognitively impaired according to the MMSE (score 27 to 30). However, the number of false positive cases should be lower as demonstrated by the MMSE.

The probability of cost-effectiveness was higher in PwD with high deficits in ADL at a WTP threshold per QALY of 0€(63% versus 24%, respectively) and 40,000€(97% versus 16%, respectively). Furthermore, compared to PwD with no cognitive deficits (according to MMSE after screening), the probability of cost-effectiveness was higher in PwD with moderate cognitive deficits at a WTP threshold per QALY of 0€(93% versus 18%, respectively) and 40,000€(100% versus 3%, respectively). Compared to PwD with low comorbidity, the probability of cost-effectiveness of the DCM was higher in PwD with high comorbidity at WTP thresholds per QALY of 0€(75% versus 37%, respectively) and 40,000€(96% versus 26%, respectively). The probabilities of cost-effectiveness for the total sample as well as for each subgroup are presented in Fig. 1.

Sensitivity analysis: Associations between different interaction terms and individual cost-effectiveness

The multivariate linear regression analyses revealed that female PwD (b = –10,873, SE = 4,775) who received the DCM caused significantly lower total healthcare cost over the 24 months' time horizon compared to females receiving care as usual. Female PwD who received the DCM caused slightly higher cost for day and night care, medication, and medical aid, but significantly lower cost for in-hospital treatments (5,579€versus 9,468€) due to fewer days stayed in a hospital (9 days versus 16 days) as well as lower cost for nursing home care (2,230€versus 4,697€) due to a delayed institutionalization (12.4 months versus 4.4 months) over a 24 months' time frame compared to female PwD receiving usual care. Furthermore, mildly (b = +0.226, SE = 0.093) or moderately cognitively impaired PwD (b = +0.232, SE = 0.105) and highly functionally impaired PwD (b = +0.200, SE = 0.095) showed a significant association with higher QALYs compared to those subgroups receiving usual care. Table 3 represents the association between different interaction terms (study group intervention # sociodemographic or clinical subgroup) and cost and effects of the DCM intervention compared to care as usual.

The interaction between receiving the intervention and female sex (b = +11,733, SE = 3,721), living

Table 2
Description of incremental cost, effect and ICER of total sample and different identified subgroups

	n (%)	Incremental cost Mean (SD; $CI^{95\%}$)	Incremental QALY Mean (SD; $CI^{95\%}$)	ICER
Overall, total sample	444 (100%)	–569€(2,491; –5,466–4,328)	+0.049 (0.045; –0.040–0.135)	DCM dominates (–11,612€/QALY)
Age				
young (<80 y)	200 (45.0%)	+2,425€(3,162; –3,811–8,662)	+0.069 (0.067; –0.063–0.200)	35,145€/QALY
old (>80 y)	244 (55.0%)	–3,716€(3,701; –11,008–3,574)	+0.039 (0.057; –0.074–0.152)	DCM dominates (–95,282€/QALY)
Sex				
male	177 (39.9%)	+4,911€(3,266; –1,536–11,359)	+0.069 (0.076; –0.081–0.218)	71,173€/QALY
female	267 (60.1%)	–4,307€(3,488; –11,175–2,560)	+0.036 (0.052; –0.067–0.140)	DCM dominates (–119,639€/QALY)
Living situation				
living alone	224 (50.5%)	–3,642€(3,938; –11,405–4,120)	+0.034 (0.063;–0.091–0.159)	DCM dominates (–107,118€/QALY)
living not alone	220 (49.5%)	+1,799€(3,020; –4,153 –7,752)	+0.067 (0.060; –0.052–0.186)	26,851€/QALY
Deficits in Daily Living Activities (B-ADL)				
no	158 (35.6%)	+668€(3,184; –5,622–6,958)	+0.032 (0.057; –0.082–0.147)	20,414€/QALY
mild	162 (36.5%)	–2,678€(4,977; –12,506–7,155)	+0.053 (0.070; –0.085–0.192)	DCM dominates (–50,528€/QALY)
high	124 (27.9%)	–3,472€(3,882; –11,158–4,213)	+0.159 (0.091; –0.023–0.341)‡	DCM dominates (–21,836€/QALY)
Cognitive Deficits (MMSE)				
no indication	99 (22.3%)	+5,485€(3,055; –577–11,547)‡	–0.147 (0.083; –0.313–0.019)‡	Usual Care dominates (–37,313€/QALY)
mild	227 (51.1%)	–648€(3,955; –8,442–7,145)	+0.109 (0.059; –0.008–0.226)‡	DCM dominates (–5,945€/QALY)
moderate to severe	118 (26.6%)	–5,574€(4,495; –14,479–3,329)	+0.102 (0.093; –0.082–0.286)	DCM dominates (–54,647€/QALY)
Comorbidity (CCI)				
low	102 (23.0%)	+2,885€(4,738; –6,515–12,285)	–0.073 (0.080; –0.234–0.087)	Usual Care dominates (–39,520€/QALY)
high	171 (38.5%)	–7,416€(4,740; –16,774–1,941)	+0.071 (0.075; –0.077–0.220)	DCM dominates (–104,451€/QALY)
very high	171 (38.5%)	+3,497€(3,410; –3,236–10,230)	+0.131 (0.071; –0.009–0.272)‡	26,694€/QALY

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; SD, standard deviation; CI, confidence interval; ‡$p < 0.01$.

Explanation:

Table 2 summarize the differences in costs and QALYs at 24 months. Compared with usual care, the dementia care management was associated with higher QALY and lower cost for the total sample after 24 months. Incremental QALY and costs indicating that the dementia care management was more likely to be less costly and more effective according to QALY. For female and alone living patients with mild deficits in daily living, mild cognitive deficits and high comorbidity the incremental costs decreased but more QALY were gained. Therefore, the dementia care management still dominates the usual care from a cost-effectiveness perspective.

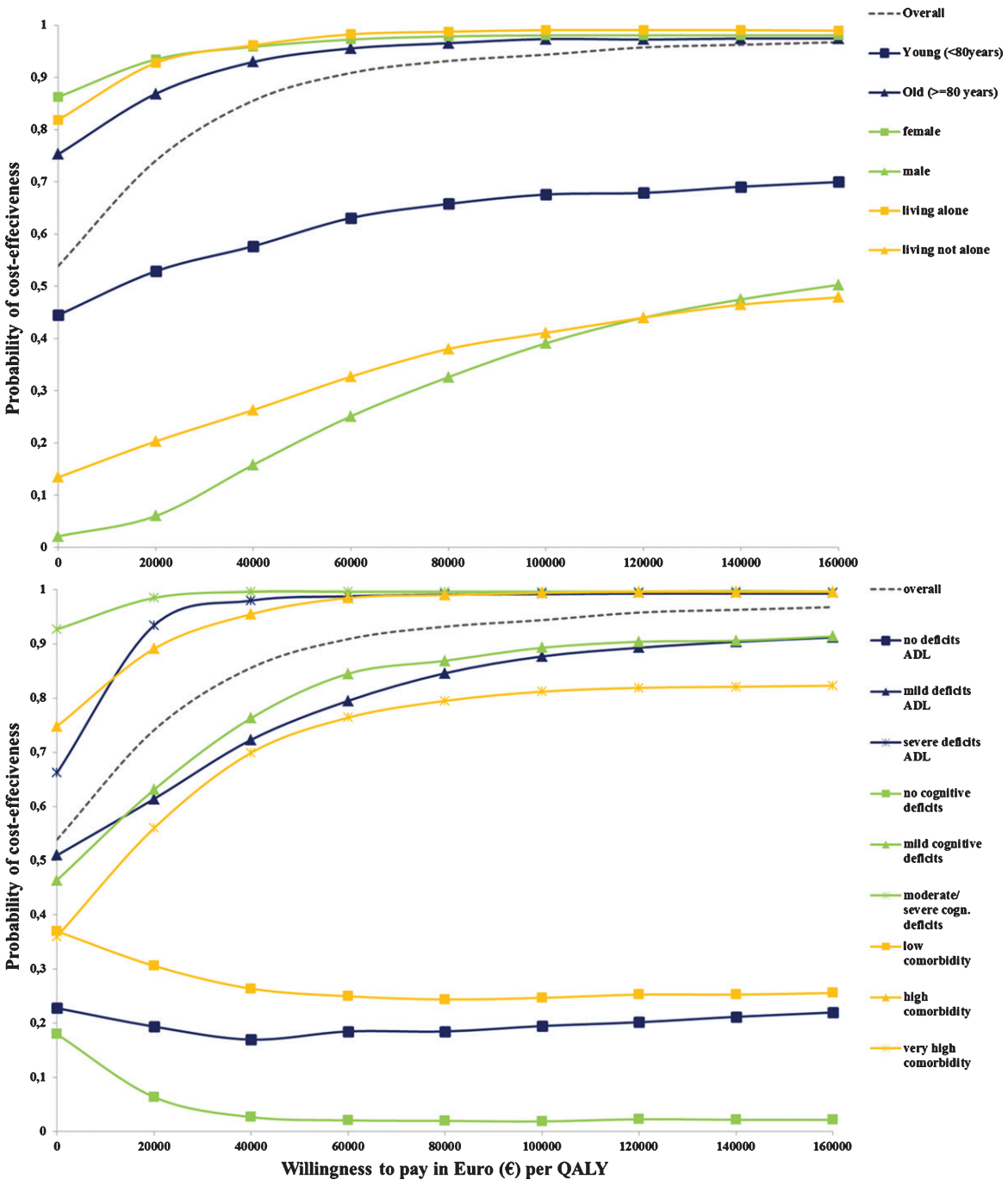

Fig. 1. Cost-effectiveness acceptability curves, DCM intervention overall and subgroups.

alone (b = +8,417, SE = 3,676), mild or moderate to severe cognitive deficits (b = +13,456, SE = 4,657; b = +12,621, SE = 5,579), as well as a high comorbidity (b = +13,007, SE = 4,607) were associated with a higher individual NMB at a willingness-to-pay threshold of 40,000€/QALY, demonstrating that the DCM was more cost-effective for these subgroups. Associations remain stable at the ceiling ratios

Table 3
Association between different interaction terms (study group intervention # sociodemographic or clinical subgroup) and cost and effects

N = 444	COSTs		QALYs	
Explanatory variables	COSTs b (SE)	QALYs $CI^{95\%}$	b (SE)	$CI^{95\%}$
Intervention				
#old (<80 y)	–7,394 (4,724)	[–16,653–1,865]	0.040 (0.734)	[–0.103–0.184]
Intercept	*12,611 (8,004)*	*[–3,076–28,299]*	*0.469 (0.196)**	*[0.085–0.852]*
#female	–10,873 (4,775)*	[–20,231–1,514]	0.048 (0.075)	[–0.100–0.196]
Intercept	*–14,848 (17,026)*	*[–48,218–18,522]*	*1.078 (0.299)****	*[0.492–1.663]*
#living alone	–8,153 (4,704)	[–17,372–1,066]	0.059 (0.073)	[–0.085–0.203]
Intercept	*–15,688 (17,004)*	*[–49,015–17,638]*	*1.020 (0.300)****	*[0.432–1.608]*
#mild deficits MMST[1]	–2,718 (5,971)	[–14,421–8,985]	0.226 (0.093)**	[0.044–0.407]
#moderate deficits MMST[1]	–11,015 (6,768)	[–24,281–2,250]	0.232 (0.105)*	[0.025–0.438]
Intercept	*–25,526 (16,643)*	*[–58,147–7,094]*	*1.203 (0.282)****	*[0.650–1.757]*
#mild deficits B-ADL[2]	–4,122 (5,438)	[–14,780–6,535]	0.086 (0.085)	[–0.080–0.251]
#high deficits B-ADL[2]	6,160 (6,100)	[–18,115–5,795]	0.200 (0.095)*	[0.014–0.386]
Intercept	*–11,786 (17,163)*	*[–45,425–21,853]*	*0.945 (0.302)***	*[0.353–1.537]*
#high comorbidity[3]	–9,026 (5,981)	[–20,749–2,698]	0.147 (0.095)	[–0.039–0.332]
#very high comorbidity[3]	1,500 (6,097)	[–10,451–13,450]	0.125 (0.103)	[–0.077–0.327]
Intercept	*–10,552 (17,054)*	*[–43,978–22,873]*	*1.033 (0.298)****	*[0.448–1.617]*

***0.001, **0.01, *0.05; [1]comparison with control group patients having no indication for cognitive impairment; [2]comparison with control group patients having no deficits in daily living activities; [3] comparison with control group patients having a low comorbidity.

80,000€ and 160,000€ but coefficients rise linear with increasing ceiling ratios.

The sensitivity analysis of the association between the interaction terms and the individual NMB for the ceiling ratio of 40,000€, 80,000€, and 160,000€(λ) is displayed in Supplementary Table 1.

DISCUSSION

In this study, we describe the cost-effectiveness of DCM for different subgroups, providing valuable information to answer our question "Who benefits most from DCM?" from a patient and payer perspective. While DCM was associated with higher QALY and lower cost for the total sample after 24 months on average, the results were not statistically compelling. In part this may be due to inadequate power as costs in general and in this case tend to be highly variable. However, it may be also due to the application of the DCM in a diverse population, with some subjects more or less likely to respond to the intervention with improved outcomes and reduced costs. In our subgroup analyses, we suggested that DCM was especially promising for specific subgroups, specifically for women, people living alone, and people with higher comorbidity and higher cognitive and functional deficits. Particularly notable is that our findings were confirmed within linear regression models using interaction terms and the individual NMB of each PwD.

The DCM was more cost-effective in female PwD due to significantly lower costs for in-hospital treatment and nursing home care over a 24 months' time frame. In addition, the DCM was more cost-effective in patients living alone, especially due to fewer physician visits and thereby significantly lower healthcare utilization and costs for treatment and care. PwD with mild and moderate to severe cognitive deficits, high functional deficits, and high comorbidity gained significantly more QALYs than patients without cognitive and functional deficits and low comorbidity.

The result that patients living alone benefit more from DCM is intuitive since patients not living alone received often more support and care from their relatives. Their needs are usually detected through the caregiver, who often lives in the same household. Because patients living alone have more often no relatives or caregivers able to provide informal care needed to maintain as long as possible at home. These PwDs can benefit most from a collaborative care management due to their higher number of unmet needs that could be addressed. In particular, arranging day and night care services as well as ambulatory care services could prevent unnecessary hospital-

ization and delay the institutionalization. Therefore, patients living alone showed lower incremental cost and higher incremental effects when their individual unmet needs were adequately addressed, as part of the DCM.

We found that female PwD who received the DCM caused lower cost and had higher QALY than male patients. The relatively higher net benefit for female within the sensitivity analysis implies that the value of the incremental benefit exceeded the incremental costs. The reasons could be the same as for patients living alone: Because female patients at a high age probably might have more often fewer relatives or carers, were living alone, and had high number of unmet needs. Thus, females can benefit more from collaborative care management programs. In addition, female patients receiving the collaborative care management had significantly lower cost for in-hospital treatments due to fewer days stayed in a hospital as well as lower cost for nursing home care due to delayed institutionalization.

In addition, PwD with a high comorbidity experience lower incremental costs and more QALYs through the intervention as PwD with low or very high comorbidity. Thus, for PwD with high comorbidity the dementia care management still dominates the usual care from a cost-effectiveness perspective. In our previous analysis, we identified a non-linear distribution of costs between the comorbidity subgroups and detects the lowest total costs in PwD with a high comorbidity [47]. Our present cost-effectiveness analysis demonstrates the same tendency. The probability of cost-effectiveness of the DCM was higher in PwD with a high comorbidity compared to PwD with a low or very high comorbidity. It could be supposed that comorbidities in PwD are underreported, which may also point to an inappropriate management of the comorbidities and that intensive treatment of some comorbidities in dementia patients is inappropriate. This possibly indicates that treatment and care for PwD with high comorbidity is not as extensive as for those without complex needs. Thus, PwD with high comorbidity might have more unmet needs and can benefit more from a DCM through addressing these unmet needs adequately.

The sensitivity analysis with the NMB approach is consistent with the results of the multivariate approach; however, the NMB approach involves both cost and effectiveness estimates, and it would be incorrect to infer that the net-monetary benefits are significant simply because the corresponding coefficients from the cost and effect equations were individually significant [63]. However, the subgroups of female PwD, PwD with mild or moderate to severe cognitive deficits as well as PwD with high deficits in activities of daily living revealed as well significant NMB values. It could be assumed, that these subgroups showed higher and significant individual NMB due to lower significant incremental cost or higher significant incremental effects in the multivariate model. In addition, the NMB approach demonstrated more significant results in some selected subgroups than the multivariate approach. The association between different interaction terms and individual net monetary benefit with ceiling ratios of 40,000€, 80,000€, and 160,000€indicated additionally significant NMB values for patients living alone and for PwD with a high comorbidity. However, the NMB method revealed no substantive changes in the results of the multivariate approach and confirmed the results of the cost-effectiveness acceptability curves.

Several studies evaluated the cost-effectiveness of DCM [64–70]. For dementia care or case management programs, only a few studies provide details on the cost-effectiveness compared to care as usual. For example, one study from the Netherlands evaluated the cost-effectiveness of two different types of case management compared to usual care. The results showed that less QALY were gained compared to usual care [71]. Another study of care-coordination of dementia patients showed a non-significant decrease of QALY as well [17]. These results are not equivalent to our findings. The patients in these trials were significantly more cognitively impaired. Consequently, the DCM was initiated later in the progression of dementia diseases. This could be an explanation for the finding of lower cost-effectiveness of previously published studies.

Another study assessed the cost-effectiveness of community-based occupational therapy compared with usual care in older patients with dementia. The results revealed that the intervention is cost-effective compared to care as usual [72]. The results are comparable to our findings. Furthermore, one analysis evaluated the cost-effectiveness with the NMB framework for preventive home visits in older people. The study evaluated the cost-effectiveness of preventive home visits. Costs and QALY were higher in the intervention group, but differences were not significant. For preventive home visits at a WTP per QALY of 50,000 EUR, there is a 15% probability that the intervention would be deemed cost-effective

[73]. However, the results of these analyses are not readily comparable to the demonstrated results of our study as well due to the different sample characteristics and considerable differences in the intervention. In addition, most of the previous studies did not focus on important subgroups and did not analyze the individual cost-effectiveness. To our knowledge, there is presently no other study that detects subgroups of PwD who could benefit most from a DCM.

Because dementia is not curable today, there is a need for optimum treatment and care for those being affected by dementia. The increasing number of PwD is a major challenge for the health care system and society due to the increasing utilization of health care resources and the associated high healthcare expenditures [5, 6]. That is the reason why it is important to provide optimal support and evidence-based treatment for the affected patients to improve their living and care situation and to enable PwD to stay in their own home as long as possible. Innovative collaborative care models for PwD have met several of these challenges, and have been successful in the provision of optimal support and evidence-based treatment.

Our results provide detailed information on the costs and effects for specific patient groups that could benefit most from a dementia care management. They can, thus, support the implementation into routine care.

Due to demographic and societal transition, the number of PwD living alone increased. As a result of the aging population, there is an increasing number of especially female PWD who do not have any relative, friend, or neighbor close by who can take care of them. Eichler et al. (2016) revealed the high proportion of PwD living alone in Germany and demonstrated that PwD living alone were significantly more often female and older and have more unmet needs, less access to health care, untreated medical conditions, and earlier nursing home transition [74]. For those PwD, the DCM is a potential solution to achieve optimal coordination and management of treatment and care. Our result revealed that for the growing subgroup of females and alone-living PwD, a collaborative care management could be very beneficial by improving certain outcomes. Identifying subgroups for whom DCM is an especially good value could be of vital importance for decision makers in the health care system in order to improve the allocation of resources in face of the increasing economic burden due to dementia diseases.

Limitations

Several limitations of the study have to be taken into consideration. Firstly, the DelpHi-trial was conducted in Mecklenburg Western Pomerania, a mostly rural area in Germany. The generalizability of the results might be limited due to the region under analysis. However, due to the population-based design with GPs in a leading role, our results will likely extend to other regions, at least to those with similar characteristics.

Second, the number of patients between the intervention and control group was not adequately balanced. Due to the impossibility to blind the intervention, patients in the control group withdrew the informed consent more frequently. In addition, there are differences between the group sizes of selected subgroups. To reduce uncertainty in the estimation procedure, we used non-parametric bootstrapping with 2,000 replications and stratified for cluster and group distribution. Nevertheless, the different group sizes in some subgroups could have affected the results.

As shown in our previous cost-effectiveness analysis of the DelpHi-MV trial, drop out was significantly associated with being in the control group and very likely before starting the baseline assessment ($n = 118$ of 634, representing 19% of the total sample). GPs were not informed about their randomization status but become aware of their status during the course of the study due to the nature of the intervention. This could have led to a decreased motivation for the recruitment in the control group and thus to the higher drop out in controls before starting the baseline assessment. In addition, a lower comorbidity and a higher functional impairment of the PwD as well as a nonparticipation of the caregiver were significantly associated with a drop out. (Drop-out analyses presented in the trial flowchart were published elsewhere [7].) However, as pointed out in the result section, there were no significant group differences regarding sociodemographic and clinical data at baseline.

Third, we collected the healthcare resource use data via comprehensive standardized computer-assisted personal interviews and analyzed the self-reported information about utilization retrospectively for a period of one year. There might be a recall-bias that could lead to an under- or overestimation of the utilization. However, more comprehensive primary data from health insurances were not available and a national health institute does not exist in Germany. To minimize gaps in the self-report, the

study assistants were trained to ask for proxy estimates as well wherever a caregiver was available.

Lastly, the net-benefit regression results depend on the maximum WTP per unit of effect. In general, there is a great difficulty in obtaining the WTP information. Caution should be exercised when normative statements are based on those values. Due to the controversy about which ceiling ratio to use, we calculate a series of NMB values by using a huge range of cost-effectiveness ceiling ratios. The cost-effectiveness acceptability curve offers a convenient presentation of cost-effectiveness results for a range of threshold values of additional health benefits. However, the net-benefit framework has the same limitations as traditional cost-effectiveness analyses.

Conclusion

This analysis indicates that the cost-effectiveness of DCM significantly differs in consideration of several subgroups. Collaborative care may be especially valuable for specific subgroups allowing tailoring such programs to PwD most likely to achieve significant cost savings and gains in QALYs. Specifically, we showed that women, PwD who were living alone, and PwD with a high comorbidity could benefit most from a DCM. For these subgroups, the DCM shows the highest individual cost-effectiveness compared to the usual care. Furthermore, PwD that were moderate to severely cognitively or functionally impaired achieved a higher gain in QALYs due to the DCM. Implementation of DCM into routine care could be most beneficial for these patients.

ACKNOWLEDGMENTS

This study is part of the DelpHi-MV trial (Dementia: Life- and person-centered help in Mecklenburg-Western Pomerania) and was funded by the German Center for Neurodegenerative Diseases (DZNE) and the University Medicine of Greifswald. Development, coordination and implementation of the DelpHi-MV study were influenced by input from several experts in their respective field and supported by an experienced field study team.

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/19-0578r5).

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-190578.

REFERENCES

[1] Prince M, Albanese E, Guerchet M, Prina M (2014) *World Alzheimer Report 2014. Dementia and risk reduction: An analysis of protective and modifiable risk factors*, Alzheimer's Disease International, London.

[2] Bickel H, Die Häufigkeit von Demenzerkrankungen [Frequencies of dementia illnesses], https://www.deutsche-alzheimer.de/fileadmin/alz/pdf/factsheets/infoblatt1_haeufigkeit_demenzerkrankungen_dalzg.pdf, Accessed April 16, 2019.

[3] Satizabal CL, Beiser AS, Chouraki V, Chêne G, Dufouil C, Seshadri S (2016) Incidence of dementia over three decades in the Framingham Heart Study. *N Engl J Med* **374**, 523-532.

[4] Kricheldorff C, Hewer W (2016) Versorgung von Menschen mit Demenz im gesellschaftlichen Wandel. *Z Gerontol Geriatr* **49**, 179-180.

[5] Förstl H (2005) *Demenzen: Perspektiven in Praxis und Forschung*, Elsevier, Urban & Fischer.

[6] Bickel H (2001) Demenzen im höheren Lebensalter: Schätzungen des Vorkommens und der Versorgungskosten. *Z Gerontol Geriatr* **34**, 108-115.

[7] Michalowsky B, Xie F, Eichler T, Hertel J, Kaczynski A, Kilimann I, Teipel S, Wucherer D, I. Z, Thyrian JR, Hoffmann W (2019) Cost-effectiveness of dementia care management alongside a cluster-randomized controlled interventional DelpHi-Trial. *Alzheimers Dement* **15**, 1296-1308.

[8] Reilly S, Miranda-Castillo C, Malouf R, Hoe J, Toot S, Challis D, Orrell M (2015) Case management approaches to home support for people with dementia. *Cochrane Database Syst Rev* **1**, CD008345.

[9] Thyrian JR, Hertel J, Wucherer D, Eichler T, Michalowsky B, Dreier-Wolfgramm A, Zwingmann I, Kilimann I, Teipel S, Hoffmann W (2017) Effectiveness and safety of dementia care management in primary care: A randomized clinical trial. *JAMA Psychiatry* **74**, 996-1004.

[10] Thyrian JR, Fiss T, Dreier A, Bowing G, Angelow A, Lueke S, Teipel SJ, Flessa S, Grabe HJ, Freyberger HJ, Hoffmann W (2012) Life- and person-centred help in Mecklenburg-Western Pomerania, Germany (DelpHi): Study protocol for a randomised controlled trial. *Trials* **13**, 56.

[11] Eloniemi-Sulkava U, Notkala I-L, Hentinen M, Kivelä S-L, Sivenius J, Sulkava R (2001) Effects of supporting community-living demented patients and their caregivers: A randomized trial. *J Am Geriatr Soc* **49**, 1282-1287.

[12] Vickrey BG, Mittman BS, Connor KI, Pearson ML, la Penna RD, Ganiats TG, Demonte RW Jr, Chodosh J, Cui X, Vassar S, Duan N, Lee M (2006) The effect of a disease management intervention on quality and outcomes of dementia care: A randomized, controlled trial. *Ann Intern Med* **145**, 713-726.

[13] Miller R, Newcomer R, Fox P (1999) Effects of the Medicare Alzheimer's Disease Demonstration on nursing home entry. *Health Serv Res* **34**, 691-714.

[14] Newcomer R, Miller R, Clay T, Fox P (1999) Effects of the Medicare Alzheimer's disease demonstration on Medicare expenditures. *Health Care Financ Rev* **20**, 45-65.

[15] Callahan CM, Boustani MA, Unverzagt FW, Austrom MG, Damush TM, Perkins AJ, Fultz BA, Hui SL, Counsell SR, Hendrie HC (2006) Effectiveness of collaborative care for older adults with Alzheimer disease in primary care: A randomized controlled trial. *JAMA* **295**, 2148-2157.

[16] MacNeil VJ, Bosmans JE, van d, V, Joling KJ, van Mierlo LD, Meiland FJ, Moll van Charante EP, van Hout HP, de Rooij SE (2015) Community-dwelling patients with demen-

tia and their informal caregivers with and without case management: 2-year outcomes of a pragmatic trial. *J Am Med Dir Assoc* **16**, 800-808.

[17] Meeuwsen E, Melis R, van der Aa G, Golüke-Willemse G, de Leest B, van Raak F, Schölzel-Dorenbos C, Verheijen D, Verhey F, Visser M, Wolfs C, Adang E, Olde Rikkert M (2013) Cost-effectiveness of one year dementia follow-up care by memory clinics or general practitioners: Economic evaluation of a randomised controlled trial. *PLos One* **8**, e79797.

[18] Eichler T, Thyrian JR, Dreier A, Wucherer D, Kohler L, Fiss T, Bowing G, Michalowsky B, Hoffmann W (2014) Dementia care management: Going new ways in ambulant dementia care within a GP-based randomized controlled intervention trial. *Int Psychogeriatr* **26**, 247-256.

[19] Dreier A, Thyrian JR, Eichler T, Hoffmann W (2016) Qualifications for nurses for the care of patients with dementia and support to their caregivers: A pilot evaluation of the dementia care management curriculum. *Nurse Educ Today* **36**, 310-317.

[20] Eichler T, Thyrian JR, Fredrich D, Köhler L, Wucherer D, Michalowsky B, Dreier A, Hoffmann W (2014) The benefits of implementing a computerized Intervention-Management-System (IMS) on delivering integrated dementia care in the primary care setting. *Int Psychogeriatr* **26**, 1377-1385.

[21] Calabrese P, Kessler J (2000) Screening for cognitive impairment in dementia - the DemTect procedure. *Eur Neuropsychopharmacol* **10**, 369.

[22] Thyrian JR, Eichler T, Michalowsky B, Wucherer D, Reimann M, Hertel J, Richter S, Dreier A, Hoffmann W (2016) Community-dwelling people screened positive for dementia in primary care: A comprehensive, multivariate descriptive analysis using data from the DelpHi-Study. *J Alzheimers Dis* **52**, 609-617.

[23] Powney M, Williamson P, Kirkham J, Kolamunnage-Dona R (2014) A review of the handling of missing longitudinal outcome data in clinical trials. *Trials* **15**, 237.

[24] Faria R, Gomes M, Epstein D, White IR (2014) A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials. *Pharmacoeconomics* **32**, 1157-1170.

[25] Thyrian J, Hertel J, Wucherer D, Eichler T, Michalowsky B, Dreier-Wolfgramm A, Zwingmann I, Kilimann I, Teipel S, Hoffmann W (2017) Effectiveness and safety of dementia care management in primary care. A randomized clinical trial. *JAMA Psychiatry* **74**, 996-1004.

[26] Hort J, O'Brien JT, Gainotti G, Pirttila T, Popescu BO, Rektorova I, Sorbi S, Scheltens P (2010) EFNS guidelines for the diagnosis and management of Alzheimer's disease. *Eur J Neurol* **17**, 1236-1248.

[27] Rabins PV, Blacker D, Rovner BW, Rummans T, Schneider LS, Tariot PN, Blass DM, McIntyre JS, Charles SC, Anzia DJ, Cook IA, Finnerty MT, Johnson BR, Nininger JE, Schneidman B, Summergrad P, Woods SM, Berger J, Cross CD, Brandt HA, Margolis PM, Shemo JP, Blinder BJ, Duncan DL, Barnovitz MA, Carino AJ, Freyberg ZZ, Gray SH, Tonnu T, Kunkle R, Albert AB, Craig TJ, Regier DA, Fochtmann LJ (2007) American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Second edition. *Am J Psychiatry* **164**, 5-56.

[28] Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin e.V.(DEGAM) (2008) *DEGAM-Leitlinie Nr 12: Demenz*, omikron publishing, Düsseldorf.

[29] Deuschl G, Maier, W, Jessen, F, Spottke, A, (2016) *S3-Leitlinie "Demenzen", Leitlinien für Diagnostik und Therapie in der Neurologie.* Deutsche Gesellschaft für Neurologie (eds.).

[30] Michalowsky B, Flessa S, Eichler T, Hertel J, Dreier A, Zwingmann I, Wucherer D, Rau H, Thyrian JR, Hoffmann W (2017) Healthcare utilization and costs in primary care patients with dementia: Baseline results of the DelpHi-trial. *Eur J Health Econ* **19**, 87-102.

[31] Michalowsky B, Thyrian JR, Eichler T, Hertel J, Wucherer D, Flessa S, Hoffmann W (2016) Economic analysis of formal care, informal care, and productivity losses in primary care patients who screened positive for dementia in Germany. *J Alzheimers Dis* **50**, 47-59.

[32] Ware J, Kosinski M, Keller SD (1996) A 12-Item Short-Form Health Survey: Construction of scales and preliminary tests of reliability and validity. *Med Care* **34**, 220-233.

[33] Kessler J, Markowitsch HJ, Denzler P (1990) *Mini-Mental-Status-Test (MMST) [German Version]*, Beltz Test GmbH, Göttingen.

[34] World Health Organization (WHO) (1993) The ICD-10 classification of mental and behavioural disorders: Diagnostic criteria for research. **Volume 2**.

[35] Gauggel S, Birkner B (1999) Validity and reliability of a German version of the Geriatric Depression Scale (GDS). *Z Klin Psychol Forsch Praxis* **28**, 18-27.

[36] Hindmarch I, Lehfeld H, de Jongh P, Erzigkeit H (1998) The Bayer Activities of Daily Living Scale (B-ADL). *Dement Geriatr Cogn Disord* **9**(Suppl 2), 20-26.

[37] White IR, Royston P, Wood AM (2011) Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med* **30**, 377-399.

[38] Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, Wood AM, Carpenter JR (2009) Multiple imputation for missing data in epidemiological and clinical research: Potential and pitfalls. *BMJ* **338**, b2393.

[39] Rubin DB, Schenker N (1991) Multiple imputation in health-care databases: An overview and some applications. *Stat Med* **10**, 585-598.

[40] Brazier JE, Roberts J (2004) The estimation of a preference-based measure of health from the SF-12. *Med Care* **42**, 851-859.

[41] Billingham LJ, Abrams KR (2002) Simultaneous analysis of quality of life and survival data. *Stat Methods Med Res* **11**, 25-48.

[42] Billingham LJ, Abrams KR, Jones DR (1999) Methods for the analysis of quality-of-life and survival data in health technology assessment. *Health Technol Assess* **3**, 1-152.

[43] D'Amico F, Rehill A, Knapp M, Aguirre E, Donovan H, Hoare Z, Hoe J, Russell I, Spector A, Streater A (2015) Maintenance cognitive stimulation therapy: An economic evaluation within a randomized controlled trial. *J Am Med Dir Assoc* **16**, 63-70.

[44] Søgaard R, Sørensen J, Waldorff FB, Eckermann A, Buss DV, Phung KT, Waldemar G (2014) Early psychosocial intervention in Alzheimer's disease: Cost utility evaluation alongside the Danish Alzheimer's Intervention Study (DAISY). *BMJ Open* **4**, e004105.

[45] Byford S, Torgerson DJ, Raftery J (2000) Economic note: Cost of illness studies. *BMJ* **320**, 1335.

[46] Bock JO, Brettschneider C, Seidl H, Bowles D, Holle R, Greiner W, Konig HH (2015) [Calculation of standardised unit costs from a societal perspective for health economic evaluation]. *Gesundheitswesen* **77**, 53-61.

[47] Kaczynski A, Michalowsky B, Eichler T, Thyrian JR, Wucherer D, Zwingmann I, Hoffmann W (2019) Comorbidity in dementia diseases and associated health care resources utilization and cost. *J Alzheimers Dis* **68**, 635-646.

[48] Michalowsky B, Flessa S, Eichler T, Hertel J, Dreier A, Zwingmann I, Wucherer D, Rau H, Thyrian JR, Hoffmann W (2018) Healthcare utilization and total cost from payer and societal perspective in primary care patients with dementia – Baseline results of the DelpHi-trial. *Eur J Health Econ* **19**, 87-102.

[49] Briggs AH, Gray AM (1999) Handling uncertainty in economic evaluations of healthcare interventions. *BMJ* **319**, 635-638.

[50] Willan AR, Briggs AH (2006) *Statistical analysis of cost-effectiveness data*, Chichester & Hoboken.

[51] Manca A, Hawkins N, Sculpher MJ (2005) Estimating mean QALYs in trial-based cost-effectiveness analysis: The importance of controlling for baseline utility. *Health Econ* **14**, 487-496.

[52] Desgagne A, Castilloux AM, Angers JF, LeLorier J (1998) The use of the bootstrap statistical method for the pharmacoeconomic cost analysis of skewed data. *Pharmacoeconomics* **13**, 487-497.

[53] Obenchain RL (1999) Resampling and multiplicity in cost-effectiveness inference. *J Biopharm Stat* **9**, 563-582.

[54] Neumann PJ, Cohen JT, Weinstein MC (2014) Updating cost-effectiveness–the curious resilience of the $50,000-per-QALY threshold. *N Engl J Med* **371**, 796-797.

[55] Grosse SD (2008) Assessing cost-effectiveness in healthcare: History of the $50,000 per QALY threshold. *Expert Rev Pharmacoecon Outcomes Res* **8**, 165-178.

[56] Ramsey S, Willke R, Briggs A, Brown R, Buxton M, Chawla A, Cook J, Glick H, Liljas B, Petitti D, Reed S (2005) Good research practices for cost-effectiveness analysis alongside clinical trials: The ISPOR RCT-CEA Task Force report. *Value Health* **8**, 521-533.

[57] StataCorp S (2009) *Release 11. Statistical Software*, StataCorp LP, College Station, TX.

[58] De Ridder A, De Graeve D (2009) Comparing the cost effectiveness of risperidone and olanzapine in the treatment of schizophrenia using the net-benefit regression approach. *Pharmacoeconomics* **27**, 69-80.

[59] Hoch JS, Briggs AH, Willan AR (2002) Something old, something new, something borrowed, something blue: A framework for the marriage of health econometrics and cost-effectiveness analysis. *Health Econ* **11**, 415-430.

[60] Zethraeus N, Johannesson M, Jonsson B, Lothgren M, Tambour M (2003) Advantages of using the net-benefit approach for analysing uncertainty in economic evaluation studies. *Pharmacoeconomics* **21**, 39-48.

[61] Zethraeus N, Johannesson M, Jönsson B, Löthgren M, Tambour M (2003) Advantages of using the net-benefit approach for analysing uncertainty in economic evaluation studies. *Pharmacoeconomics* **21**, 39-48.

[62] Desgagné A, Castilloux A-M, Angers J-F, Le Lorier J (1998) The use of the bootstrap statistical method for the pharmacoeconomic cost analysis of skewed data. *Pharmacoeconomics* **13**, 487-497.

[63] Willan AR, Briggs AH, Hoch JS (2004) Regression methods for covariate adjustment and subgroup analysis for non-censored cost-effectiveness data. *Health Econ* **13**, 461-475.

[64] Jönsson L, Lindgren P, Wimo A, Jönsson B, Winblad B (1999) The cost-effectiveness of donepezil therapy in Swedish patients with Alzheimer's disease: A Markov model. *Clin Ther* **21**, 1230-1240.

[65] Banerjee S, Wittenberg R (2009) Clinical and cost effectiveness of services for early diagnosis and intervention in dementia. *Int J Geriatr Psychiatry* **24**, 748-754.

[66] Neumann P, Hermann R, Kuntz K, Araki S, Duff S, Leon J, Berenbaum P, Goldman P, Williams L, Weinstein M (1999) Cost-effectiveness of donepezil in the treatment of mild or moderate Alzheimer's disease. *Neurology* **52**, 1138-1138.

[67] Romeo R, Knapp M, Hellier J, Dewey M, Ballard C, Baldwin R, Bentham P, Burns A, Fox C, Holmes C (2013) Cost-effectiveness analyses for mirtazapine and sertraline in dementia: Randomised controlled trial. *Br J Psychiatry* **202**, 121-128.

[68] Wimo A (2004) Cost effectiveness of cholinesterase inhibitors in the treatment of Alzheimer's disease. *Drugs Aging* **21**, 279-295.

[69] Knapp M, Thorgrimsen L, Patel A, Spector A, Hallam A, Woods B, Orrell M (2006) Cognitive stimulation therapy for people with dementia: Cost-effectiveness analysis. *Br J Psychiatry* **188**, 574-580.

[70] Katon W, Russo J, Lin EH, Schmittdiel J, Ciechanowski P, Ludman E, Peterson D, Young B, Von Korff M (2012) Cost-effectiveness of a multicondition collaborative care intervention: A randomized controlled trial. *Arch Gen Psychiatry* **69**, 506-514.

[71] Vroomen JM, Bosmans JE, van de Ven PM, Joling KJ, van Mierlo LD, Meiland FJM, van Charante EPM, van Hout HPJ, de Rooij SE (2015) Community-dwelling patients with dementia and their informal caregivers with and without case management: 2-year outcomes of a pragmatic trial. *J Am Med Dir Assoc* **16**, 800.e1-8.

[72] Graff MJ, Adang EM, Vernooij-Dassen MJ, Dekker J, Jönsson L, Thijssen M, Hoefnagels WH, Rikkert MGO (2008) Community occupational therapy for older patients with dementia and their care givers: Cost effectiveness study. *BMJ* **336**, 134-138.

[73] Brettschneider C, Luck T, Fleischer S, Roling G, Beutner K, Luppa M, Behrens J, Riedel-Heller SG, König H-H (2015) Cost-utility analysis of a preventive home visit program for older adults in Germany. *BMC Health Serv Res* **15**, 141.

[74] Eichler T, Hoffmann W, Hertel J, Richter S, Wucherer D, Michalowsky B, Dreier A, Thyrian JR (2016) Living alone with dementia: Prevalence, correlates and the utilization of health and nursing care services. *J Alzheimers Dis* **52**, 619.

[75] Mackin RS, Ayalon L, Feliciano L, Areán PA (2010) The sensitivity and specificity of cognitive screening instruments to detect cognitive impairment in older adults with severe psychiatric illness. *J Geriatr Psychiatry Neurol* **23**, 94-99.

[76] Kohn N, Kalbe E, Georg H, Kessler J (2007) Vergleich MMST und DemTect: Spezifität und Sensitivität bei primär kognitiven Störungen. *Akt Neurol* **34**, P672.

Acknowledgements

This study is part of the DelpHi-MV trial (Dementia: Life- and person-centered help in Mecklenburg-Western Pomerania) and was funded by the German Center for Neurodegenerative Diseases (DZNE) and the University Medicine of Greifswald.

I would like to express appreciation to all study participants and their general practitioners for their cooperation.

Furthermore, I would like to thank the experts who contributed to the development of the study. These are, in alphabetical order: Ines Abraham, Kerstin Albuerne, Aniela Angelow, Grit Aßmann, Vaska Böhmann, Georgia Böwing, Kathleen Dittmer, Adina Dreier-Wolfgramm, Thomas Fiß, Daniel Fredrich, Sarah Gardzella, Jana Hubert, Ulrike Kempe, Viktoriya Kim-Boese, Leonore Köhler, Julius Krause, Saskia Moll, Andrea Pooch, Melanie Reimann, Sabine Schmidt and Christine Winckler.

Especially, I would like to thank those scientific colleagues who contributed substantially to the development of DelpHi-MV study, to the coordination of this study and to the recently published manuscripts, which forms the basis for this dissertation. These colleagues were, in alphabetical order: Tilly Eichler, Jochen René Thyrian, Kerstin Wernecke, Diana Wucherer, Ina Zwingmann, Feng Xie.

Finally, I would like to say thank you to Dr. rer. pol. Bernhard Michalowsky, the principal investigator of health economic analyses, as well as Prof. Dr. med. Wolfgang Hoffmann, the principal investigator of the DelpHi-MV trial, who contributed substantially to the concept of the trial and provided ample advice to this dissertation.