Received: 8 February 2024 | Revised: 26 October 2024 | Accepted: 5 November 2024

DOI: 10.1002/trc2.70028

Alzheimer's & Dementia
Translational Research & Clinical Interventions

RESEARCH ARTICLE

Cost-effectiveness of a multicomponent intervention against cognitive decline

Christian Brettschneider[1] | Elżbieta Buczak-Stec[1] | Melanie Luppa[2] | Andrea Zülke[2] | Bernhard Michalowsky[3,4] | Anika Rädke[3,4] | Alexander Bauer[5] | Christine Brütting[5] | Robert P. Kosilek[6] | Isabel Zöllinger[6] | Juliane Döhring[7] | Martin Williamson[7] | Birgitt Wiese[8] | Wolfgang Hoffmann[3,4] | Thomas Frese[5] | Jochen Gensichen[6] | Hanna Kaduszkiewicz[7] | Jochen René Thyrian[3,4] | Steffi G. Riedel-Heller[2] | Hans-Helmut König[1] | the AGEWELL.DE study group

[1]Department of Health Economics and Health Services Research, Hamburg Center for Health Economics, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[2]Institute of Social Medicine, Occupational Health and Public Health (ISAP), University of Leipzig, Leipzig, Germany

[3]Institute for Community Medicine, University Medicine Greifswald (UMG), Greifswald, Germany

[4]German Centre for Neurodegenerative Diseases (DZNE), site Rostock/ Greifswald, Greifswald, Germany

[5]Institute of General Practice and Family Medicine, Martin-Luther-University Halle-Wittenberg, Halle (Saale), Germany

[6]Institute of General Practice and Family Medicine, University Hospital LMU Munich, Munich, Germany

[7]Institute of General Practice, University of Kiel, Kiel, Germany

[8]Institute for General Practice, Work Group Medical Statistics and IT-Infrastructure, Hannover Medical School, Hannover, Germany

Correspondence
PD Dr. Christian Brettschneider, Department of Health Economics and Health Services Research, Hamburg Center for Health Economics, University Medical Center Hamburg-Eppendorf, Martinistraße 52, 20251 Hamburg, Germany.
Email: c.brettschneider@uke.de

Christian Brettschneider and Elżbieta Buczak-Stec shared first authorship.

Steffi G. Riedel-Heller and Hans-Helmut König shared last authorship.

Funding information
German Federal Ministry for Education and Research, Grant/Award Numbers: 01GL1704A, 01GL1704B, 01GL1704C, 01GL1704D, 01GL1704E, 01GL1704F

Abstract

INTRODUCTION: The societal costs of dementia and cognitive decline are substantial and likely to increase during the next decades due to the increasing number of people in older age groups. The aim of this multicenter cluster-randomized controlled trial was to assess the cost-effectiveness of a multi-domain intervention to prevent cognitive decline in older people who are at risk for dementia.

METHODS: We used data from a multi-centric, two-armed, cluster-randomized controlled trial (*AgeWell.de* trial, ID: DRKS00013555). Eligible participants with increased dementia risk at baseline (Cardiovascular Risk Factors, Aging, and Incidence of Dementia/CAIDE Dementia Risk Score ≥ 9), 60–77 years of age, were recruited by their general practitioners, and assigned randomly to a multi-domain lifestyle intervention or general health advice. We performed a cost-effectiveness analysis from the societal perspective. The time horizon was 2 years. Health care utilization was measured using the "Questionnaire for Health-Related Resource Use in Older Populations." As effect measure, we used quality-adjusted life-years (QALYs) based on the 5-level EQ-

5D version (EQ-5D-5L). We calculated the incremental cost-effectiveness ratios (ICER) and cost-effectiveness acceptability curves (CEAC) using the net-benefit approach. Exploratory analyses considering women and the EQ visual analogue scale (EQ VAS) were conducted.

RESULTS: Data were available for 819 participants (mean age 69.0 [standard deviation (SD)5-level EQ-5D version 4.9]); 378 were treated in the intervention group and 441 in the control group. The participants in the intervention group caused higher costs (+€445.88 [SD: €1,244.52]) and gained additional effects (+0.026 QALY [SD: 0.020]) compared to the participants in the control group (the difference was statistically significant). The ICER was €17,149.23/QALY. The CEAC showed that the probability of the intervention being cost-effective was moderate, reaching 59% at a willingness-to-pay (WTP) of €50,000/QALY. The exploratory analyses showed promising results, especially in the female subsample.

DISCUSSION: Considering aspects like the WTP and the limited time horizon, the multi-domain intervention was cost-effective compared to general health advice.

KEYWORDS
cost-effectiveness analysis, older individuals, cognitive decline, RCT, dementia, multicomponent intervention, risk factors

Highlights

- The first German randomized controlled trial (RCT) evaluating a multicomponent approach against cognitive decline.
- We found a favorable incremental cost-effectiveness ratio.
- The probability of cost-effectiveness reached 78.6%.
- Women could be an important target group.
- A longer time horizon is needed.

BACKGROUND

Dementia represents a major challenge to global health.[1] The number of people with dementia is projected to increase from 57.4 million worldwide in 2019 to 152.8 million in 2050.[1] Dementia costs are estimated to be around 818 billion US dollars, particularly for long-term social and informal care.[2,3] Costs will continue to rise due to increasing numbers of older people and rising costs per person.[2] Evidence suggests that there are modifiable risk factors for dementia, such as depression, malnutrition, smoking, alcohol consumption, physical inactivity, and social isolation.[4] Interventions have been developed to address several risk factors simultaneously.[5–8] The evidence concerning their effectiveness is conflicting.[5,7–9] It is important to consider that this might be the result of the characteristics of these complex interventions and not a flaw in the concept.

AgeWell.de was the first large randomized controlled trial in Germany to investigate a multi-domain intervention aimed at maintaining cognitive function in older adults.[10] Inspired by the effective Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) from 2014,[6] AgeWell.de extended this program. AgeWell.de had beneficial effects on directly-rated health-related quality of life (HRQOL) and depressive symptoms in the female subsample.[11] In a secondary analysis, dementia risk measured by the LIfestyle for BRAin health index was also reduced.[12] It was not the first study to address cognitive and physical training,[5,9,13] depression,[8] or nutrition[8,9] to prevent cognitive decline; its unique feature is the combination of different measures. However, in comparison to other studies (e.g., Multidomain Alzheimer Preventive Trial [MAPT][9]), the intensity of the intervention (number and duration of contacts) was lower.

Economic evaluations focusing on multi-domain interventions to maintain cognitive functioning indicate partially promising results. For FINGER, two modeling studies over long-term time horizons identified potential for cost-effectiveness.[14,15] Kato et al. modeled combined physical and cognitive exercise programs and concluded that the programs could be cost-effective.[13] Costa et al. evaluated a multi-domain intervention incorporating cognitive stimulation, physical activity, and nutrition in a randomized controlled trial (RCT) over 3

years (MAPT).[16] They found favorable incremental cost-effectiveness ratios (ICER) results as well. The aim of this analysis was to assess the cost-effectiveness of the AgeWell.de intervention compared to general health advice to prevent cognitive decline in older people at risk of dementia in Germany over a time horizon of 2 years from the societal perspective.

1 | METHODS

1.1 | Study design and intervention

We used data from a multi-centric, two-armed, cluster-RCT (*AgeWell.de*). A health economic analysis plan was part of the grant proposal but is not publicly available. The study was conducted at five sites across Germany (Leipzig, Kiel, Greifswald, Munich, and Halle). Eligible participants were recruited by their general practitioners (GPs) from June 2018 to October 2019. Participants 60 to 77 years of age and had an increased dementia risk at baseline (according to Cardiovascular Risk Factors, Aging, and Incidence of Dementia/CAIDE Dementia Risk Score ≥9, as assessed by their GPs).[17] Exclusion criteria included conditions that compromised safe participation, a diagnosis of dementia, visual or hearing impairments, or insufficient German language skills.

Randomization took place at the level of GP practices. Participants were assigned to the multi-domain intervention (A) or general health advice (B) and were followed up for 2 years.

The (A) intervention focused on modifiable risk factors for cognitive decline.

1. Nutrition advice (according to the guidelines of the German Nutrition Society [DGE])
2. Monitoring of vascular risk factors
3. Physical activity enhancement (strength; balance; aerobic)
4. Cognitive training at home (tablets with NeuroNation software)
5. Recommendations about optimization of medication
6. Individually planned social activity enhancement, preceded by an assessment of the risk of social isolation
7. In case of symptoms of grief, bereavement, and/or depressive symptoms, participants received information on grief reactions, self-help groups, and other sources of help

The intervention was delivered by study nurses during two home visits (baseline, month 12) and five telephone sessions (months: 2, 4, 8, 16, and 20). During the visits, participants were instructed about the individual measures. Participants were responsible for implementing the measures in their daily lives. In the telephone sessions, participants were motivated to implement the measures and to stick to their new routines. For further details, refer to the protocol.[10,11,18]

The (B) intervention (control group) included treatment as usual and written general health advice on risk factors for dementia provided as a two-page document.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors searched for scientific literature in established databases (e.g., PubMed, Google Scholar, Web of Science). A set of modifiable risk factors for dementia has already been identified. Interventions to address these risk factors have been developed. The literature on the cost-effectiveness of these interventions is scarce.
2. **Interpretation**: The results show that the intervention is cost-effective over a course of 2 years, depending on willingness to pay. Women show high potential as target group.
3. **Future direction**: Based on the results, it is recommendable to evaluate the intervention within a population of people over a longer time horizon and in specific subgroups.

1.2 | Data collection

Data were collected by structured interviews, psychological tests, and questionnaires at baseline and follow-up after 24 months.[10] Data were collected on, among other factors, socio-demographics, health care utilization, and HRQOL (5-level EQ-5D version (EQ-5D-5L)).[19,20] Data on participants' health and diagnoses were provided by GPs.

1.3 | Measurement of costs

We analyzed costs from a societal perspective. Productivity losses were excluded because most participants were retired (78.6%; Table 1). We included professional health and nursing care services along with informal care. This encompassed inpatient and outpatient care, long-term care services, medical devices, medication, and intervention costs. We assessed health care utilization during the 24-month follow-up period using the "Questionnaire for Health-Related Resource Use in Older Populations" (FIMA).[21] A list of services is presented in the Appendix (Table A1). The recall period for resource utilization was 4 months. Total utilization was estimated by multiplying these numbers by 6. Resource use was valued in Euro (€) based on German standard unit costs (see the Appendix: Table A1).[22] Informal care costs were calculated using the replacement cost approach, whereas medication data were valued based on the German pharmacy retail price index "*Rote Liste*."[23] Intervention costs were calculated based on the opportunity cost approach. An in-person meeting took 2.5 hand a telephone contact took 1 h. The monetary valuation was based on gross labor costs per hour (€37.30) for a worker in the sector Q88 (social services—excluding nursing homes).[24] We assumed that the delivery of the intervention took 10 hours (h). Costs were inflated to the reference year 2018, using the consumer price index[25] and were not discounted, as follow-up costs were measured after only 2 years.

TABLE 1 Baseline characteristics and group comparisons between control and intervention groups (based on an imputed sample with 35 imputations).

Variables *N* (SD)/% range	Total sample (*n* = 819)	Intervention group (*n* = 378)	Control group (*n* = 441)
Age in years (mean (SD); [range])	69.0 (4.9); [60–78]	69.1 (4.9); [60–78]	69.0 (4.9); [60–78]
Sex—female	52.9%	52.7%	53.1%
Education (CASMIN)			
Low	22.1%	25.9%	18.8%
Middle	52.0%	51.9%	54.0%
High	24.9%	22.2%	27.2%
Living alone	29.1%	29.1%	29.0%
Retired (yes)	78.6%	80.5%	77%
Statutory health insurance (ref. private health insurance)	92.8%	96.3%	89.8%
BMI			
Normal	12.6%	12.2%	13.0%
Pre-obesity	32.7%	31.9%	33.4%
Obesity I	33.4%	35.6%	31.5%
Obesity II	14.9%	14.5%	15.3%
Obesity III	6.4%	5.9%	6.9%
Smoking			
Never	41.5%	42.2%	40.9%
Used to	46.8%	44.8%	48.6%
Yes	11.7%	13.0%	10.6%
Income in € (mean (SD); [range])	2188 (1282); [375–9000]	2115 (1187); [375–9000]	2250 (1357); [375–9000]
SES Points (mean (SD); [range])	11.5 (3.4); [3.3–20.4]	11.3 (3.4); [3.3–19.3]	11.7 (3.7); [3.3–20.4]
Anxiety disorder, yes (ref. no)	7.0%	5.0%	8.6%
German as mother tongue	97.8%	97.6%	98.0%
Functioning (Barthel index)	99.6 (2.4); [65–100]	99.6 (2.3); [75–100]	99.6 (2.5); [65–100]
Mild cognitive impairment	8.6%	8.2%	8.9%
Direct-rated HRQOL (EQ-VAS) (mean (SD); [range])	76.9 (15.7); [10–100]	78.3 (15.1); [10–100]	75.6 (16.1); [10–100]
Preference-based HRQOL (EQ-5D index) (mean (SD); [range])	0.904 (0.14); [0.092–1]	0.909 (0.13); [0.326–1]	0.899 (0.14); [0.092–1]
Total costs (4 months) in € (mean (SD))	1373.84 (2489.98)	1511.40 (2812.59)	1255.93 (2172.12)
GDS (mean (SD); [range])	1.5 (1.9); [0–11]	1.5 (1.9); [0–10]	1.5 (1.9); [0–11]
IADL (mean (SD); [range])	1.0 (2.9); [0–41.8]	1.0 (2.9); [0–41.8]	1.0 (2.8); [0–35]
No. of comorbidities (mean (SD); [range])	4.7 (2.3); [0–12]	4.5 (2.1); [1–13]	4.7 (2.3); [0–12]

Abbreviation: BMI, body mass index; CASMIN, Comparative Analysis of Social Mobility in Industrial Nations; GDS, Geriatric Depression Scale; HRQOL, health-related quality of life; IADLs, instrumental activities of daily living; SD, standard deviation; SES, socioeconomic status.

1.4 | Measurement of effects

As an effect measure, we used quality-adjusted life-years (QALY). QALY is calculated by multiplying survival time by a preference-based utility score. In the base case analysis, the preference-based utility was derived from the EQ-5D-5L. In addition to this EQ-5D index, which reflects the valuation of health states from the general population's perspective, the EQ-5D-5L includes the EQ visual analogue scale (EQ VAS), a scale ranging from 0 to 100 that allows patients to value their own health state directly.[19,20] The QALY calculation consisted of two steps. Because the interviews did not take place exactly after 2 years, we adjusted the timeframe of the EQ-5D index assessment to 730 days.

Subsequently, we calculated the number of QALY at follow-up, assuming a linear trend between baseline and follow-up. To do this, we added baseline score to the adjusted follow-up score and divided the sum by 2. To obtain the number of QALY over 2 years, we multiplied this figure by 2. (For further information, see the methods appendix.)

QALYs were not discounted, as we measured only one follow-up after 2 years.

1.5 | Statistical analysis

The economic evaluation was conducted according to the intention-to-treat principle. Details are published in the study protocol.[10] All participants who attended the follow-up assessment were included. Missing data (maximum missing value: "other mental disorders": 34.1%) were handled through multiple imputation by chained equations (MICE) at the item level using predictive mean matching.[26,27] In total, we created 35 data sets. The analyses were conducted using Stata 16.0 (StataCorp, College Station, Texas, USA). A significance level of 5% was used for all analyses.

1.6 | Cost-effectiveness analysis

1.6.1 | Base case analysis: Costs, QALY, and ICER

In the first step, we present the mean costs and the mean QALY (based on the EQ-5D index) per group at a descriptive level. Costs are provided as total costs and broken down into cost categories (inpatient costs, outpatient costs [outpatient physician services; outpatient non-physician services; outpatient rehabilitation; outpatient surgery], long-term care services [professional care; informal care; inpatient nursing care], devices, medication, and intervention). Differences between groups were tested for significance using generalized linear models (GLMs; gamma family; log link) two-part models (logit, GLM) for costs, as well as linear models for QALY, with costs/QALY as the dependent and group as the independent variable. We accounted for the clustered data structure by calculating robust standard errors according to the method by Huber/White.

To present a point estimate of the cost-effectiveness, we will calculate the ICER. The ICER is a ratio that consists of the difference in total costs between groups in the numerator, and the effect (QALY) difference in the denominator:

$$\mathrm{ICER} = \frac{\overline{\mathrm{costs}_{\mathrm{intervention}}} - \overline{\mathrm{costs}_{\mathrm{control}}}}{\overline{\mathrm{effects}_{\mathrm{intervention}}} - \overline{\mathrm{effects}_{\mathrm{control}}}} = \frac{\Delta\overline{\mathrm{costs}}}{\Delta\overline{\mathrm{effects}}}$$

1.6.2 | Base case analysis: Uncertainty

To illustrate the uncertainty of the ICER as a point estimate, we calculated a cost-effectiveness acceptability curve (CEAC) by estimating a series of net benefit regressions (NBRs).[28,29] In an NBR, the net-monetary benefit (NMB) at different willingness to pay (WTP) thresholds is used as the dependent variable, with group as the independent variable. The NMB is defined as $NB_i = E_i \times \lambda - C_i$ where E_i represents the individual 24-month QALY, C_i the individual 24-month total costs, and λ a WTP threshold described as € per QALY. Regression models using increasing WTP thresholds (range: €0–€150,000 per QALY; increasing by €10,000 in each step) were calculated successively. The analyses were based on linear regression models and adjusted for costs and the EQ-5D index at baseline. We calculated robust standard errors according to the method by Huber/White. (For further information, see the methods appendix.)

1.6.3 | Exploratory post hoc analyses

Following the results of the effectiveness study,[11] we decided to perform three exploratory post hoc analyses:

1. Base case analysis using the direct-rated EQ VAS to determine QALY. To calculate QALY and derive HRQOL weights from the EQ VAS, we divided the score by 100.
2. Base case analysis using depression (Geriatric Depression Scale [GDS]) in the female subsample. The ICER represents the ratio of € per point improvement on the GDS. The CEAC was calculated for WTP from €0 to €15,000 per point of improvement.
3. Base case analysis using the EQ-5D index to determine QALY in the female subsample.
4. Base case analysis using the EQ-5D index to determine QALY considering only participant adherent to the AgeWell.de intervention ($n = 289$)

2 | RESULTS

2.1 | Study design and participants

Data were available for 819 participants: 378 in the intervention group (59 clusters; median size: 6) and 441 in the control group (58 clusters; median size: 6) (Figure A1 in the Appendix). At baseline, the mean age was 69.0 (standard deviation (SD) 4.9) years, 52.9% were female, and 29.1% lived alone. The control group differed from the intervention group in terms of education, EQ VAS, statutory health insurance membership, and diagnosis of an anxiety disorder. The average EQ-5D index was 0.904 (SD 0.14) (Table 1).

2.2 | Costs, effects, and ICER

After 24 months, the intervention group had higher total costs (€8,868.31 [SD 16,740.39]) compared to the control group (€8,422.43 [SD 17,950.22]) (Table 2). Most costs were attributed to outpatient costs (29.5% and 32.3%; intervention group and control group, respectively), medication costs (32.7% and 29.0%), and inpatient costs (20.2% and 21.7%). At 24 months, the average utility based on the EQ-5D index was 0.908 (SD 0.136) for the intervention group and 0.892 (SD 0.161) for the control group leading to average QALY of 1.817 (SD 0.230) for the intervention group and 1.791 (SD 0.262) for the control group.

TABLE 2 Costs, effects, and ICER after 24 months (based on MI data with 35 imputations).

	Intervention ($n = 378$)		Control group ($n = 441$)	
Category	Mean	SD	Mean	SD
Costs[a]:				
Inpatient costs	€1786.67	9310.65	€1828.88	11,775.29
Outpatient costs	€2618.60	3263.52	€2728.24	3170.67
Outpatient physician services	€1735.97	1853.79	€1865.26	2108.68
Outpatient non-medical care	€701.18	1231.75	€733.63	1730.88
Outpatient rehabilitation	€120.92	1959.60	€18.72	317.18
Outpatient surgery	€60.54	427.60	€110.63	764.29
Long-term care services	€933.62	7949.21	€1,346.53	9,840.78
- Professional care (outpatient nursing services)	€133.55	914.68	€505.89	4,855.26
Informal care	€460.97	4380.59	€840.64	5935.80
Inpatient nursing care	€339.10	6101.95	€0	0
Medication	€2902.79	8191.63	€2440.96	5359.92
Devices costs	€253.63	1346.59	€77.82	656.96
Intervention costs	€373.00	-	€0	-
Total costs	€8868.31	16,740.39	€8422.43	17,95022
Effects:				
QALY (EQ-5D-5L)	1.815	0.229	1.791	0.262
QALY (EQ VAS)	1.564	0.263	1.494	0.287
ICER (/ QALY: EQ-5D-5L)	€17,149.23 / QALY (= €445.88/0.026)			
ICER (/ QALY: EQ VAS)	€6557.06 / QALY (= €445.88/0.068)			

Abbreviation: EQ-5D-5L, 5-level EQ-5D version; EQ VAS, EQ visual analogue scale; ICER, unadjusted incremental cost-effectiveness ratio; QALY, quality-adjusted life years; SD, standard deviation.
[a]Based on 2018 Euros.

The group cost difference was €445.88 (SD 1,243.77) and the group QALY difference was 0.026 (SD 0.020), neither of which was statistically significant. The ICER was €17,149.23/QALY.

2.3 | Uncertainty of cost-effectiveness

The probability of the intervention being cost-effective was moderate. At a WTP of €50,000 per QALY, this probability was 59.0%, ranging from 39.3% at a WTP of €0 per QALY to 78.6% at a WTP of €150,000 per QALY gained (Figure 1).

2.4 | Exploratory post hoc analyses

1. EQ VAS: The average EQ VAS score before weight calculation was 78.1 in the intervention group and 73.8 in the control group. The ICER was €6557.06 per QALY gained through the intervention. The CEAC ranged from 30.1% (WTP €0 per QALY) to 96.6% (WTP €150,000 per QALY). At €50,000 per QALY, the probability of cost-effectiveness was 72.7% (Figure 1).
2. Women, GDS: The ICER indicated dominance (i.e., lower costs and better effects) of the intervention. For specific cost and effect data see Table A2 (Appendix). The CEAC ranged from 74.1% (WTP €0 per point improvement) to 98.2% (WTP €15,000). A probability of 95% was reached at a WTP of €7000 (Figure 1).
3. Women, EQ-5D index: The intervention dominated the control according to the ICER (Table A2 Appendix). The CEAC ranged from 73.1% (WTP €0 per QALY) to 84.5% (WTP of €150,000). At a WTP of €50,000, the probability was 86.7% (Figure 1).
4. Adherent participants: The ICER was €18,750.61 per QALY gained through the intervention (Table A3 Appendix). The CEAC ranged from 38.6% (WTP €0 per QALY) to 84.9% (WTP €150,000 per QALY). At €50,000 per QALY, the probability of cost-effectiveness was 63.2% (Figure 1).

3 | DISCUSSION

3.1 | Key results

In this study, we conducted a cost-effectiveness analysis of the first multi-domain lifestyle intervention against cognitive decline in Germany. Our analysis showed that the intervention incurred additional costs and gained QALY. Assuming the threshold of €50,000, the

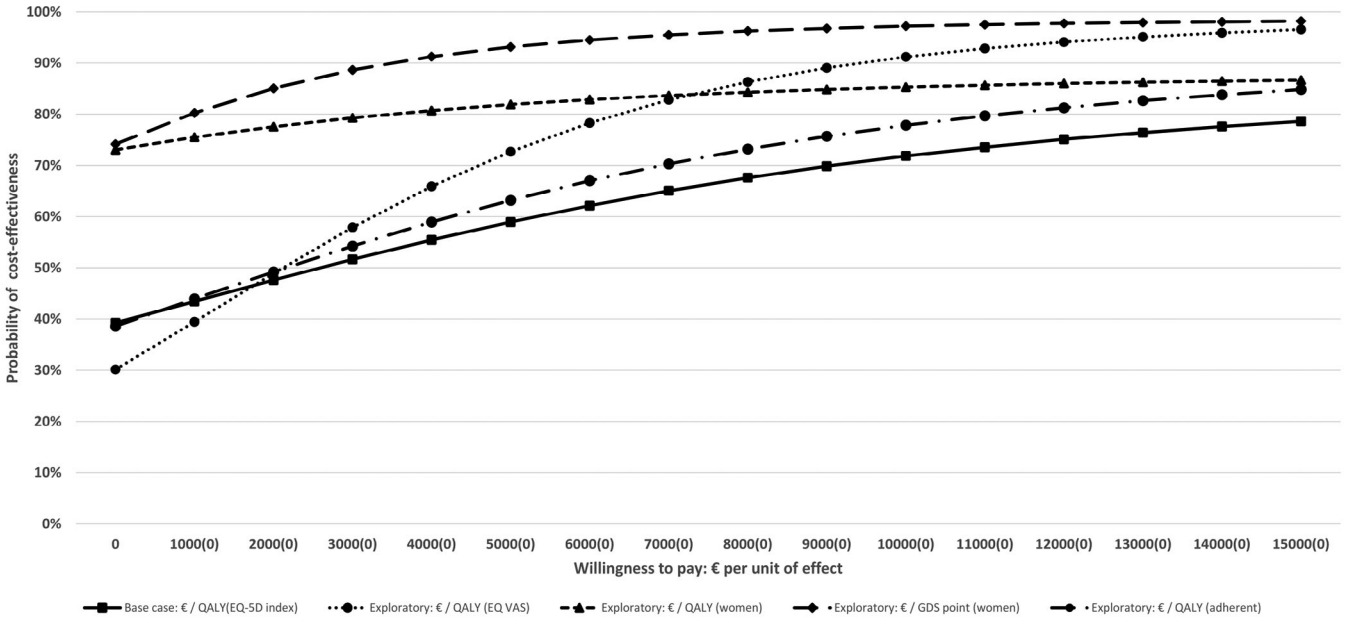

FIGURE 1 "Cost-effectiveness acceptability curve" based on total costs and QALY. QALY, quality-adjusted life-years.

resulting ICER of €17,149.23 per QALY implies cost-effectiveness. However, this conclusion is subject to uncertainty depending on WTP. Adherence had no impact on cost-effectiveness. Consequently, it depends on decision-makers, their WTP and risk preferences whether the intervention is recommendable from an economic perspective.

The analysis of the female subsample led to interesting insights as the intervention was likely to be cost-effective. At a WTP threshold of €50,000 per QALY, the probability was 82%. This identifies women as a target group.

The AgeWell.de study complements the literature as it contributes to studies showing no effect on global cognitive functioning.[7,9] However, for direct-rated HRQOL and depression it indicated a favorable effect. There has been conflicting evidence on the influence on depression.[7–9] Regarding the economic evaluation, our analysis aligns with other studies. The modeling studies conducted for the FINGER trial[14,15] and by Kato et al.[13] indicated potential benefits over a time horizon of at least 10 years. Nevertheless, the analysis by Costa et al. is particularly noteworthy that analyzed data from a 3-year RCT (MAPT).[16] They showed cost-effectiveness at a WTP threshold of €50,000 per improved *z*-score point. We were unable to reproduce this result. Various explanations exist. First, although Costa et al. assume that the WTP for an improved *z*-score point is €50,000,[16] this might not be comparable to the €50,000 per QALY threshold. Second, Costa et al. had data for a 3-year period, whereas we had data for 2 years.[16] Costa et al. showed that in the first 2 years of the study the resource utilization and costs remained quite stable, whereas they increased in year 3.[16] We did not cover this period. Third, the intervention in the study by Costa et al. had a higher intensity regarding contact number and duration.[9,16]

Nevertheless, our main results as well as the exploratory subgroup analyses show that the AgeWell.de intervention could be a promising approach needing further adaptation.

Focusing on effects and costs specifically, we found that the HRQOL stayed stable over 2 years. In the intervention group, the EQ-5D index decreased by 0.001 over the course of 24 months. In the control group, the corresponding decrease was 0.007. In interpreting these numbers, it is important to consider that the AgeWell.de intervention aimed to preserve functioning. The EQ-5D-5L assesses problems in functioning and translates them into a preference-based HRQOL index. The results indicate that over the course of 2 years the intervention had no considerable advantage in preserving functioning. The effects based on the EQ VAS show a slightly different trend. Here, the change in the intervention group was small (−0.2 points). However, in the control group, the loss was larger (−1.8 points). Because the EQ VAS is a direct measure of HRQOL that considers the health state as a whole, this difference in developments might be seen as a precursor of a change in functioning over time. This should be investigated in a study with a longer duration.

Regarding costs, the results for the long-term care sector might be of interest as an indicator of functioning. To underscore this assumption, we want to highlight a study by Neubert et al. that evaluated the excess costs of dementia in later life. This study showed that the 6-month excess costs of dementia are between €9000 and €12,000.[30] These costs were mainly for professional and informal care. In our study, the costs of informal care and professional ambulatory care services were lower in the intervention group. This could be an indicator that the intervention may have fostered functioning and independence. However, this is an assumption. It may be important to observe the development of long-term care utilization in future studies of preventive measures.

There is no cure for dementia. That is why such great expectations are placed on interventions that minimize the risk of dementia. Results from a Finnish trial (FINGER) or a Taiwanese study by Chen et al. suggest that a multi-domain intervention may preserve global

cognitive function in at-risk older individuals.[5,8] However, other evaluations of multi-domain interventions showed no significant effect.[7,9,11] Notwithstanding these inconsistencies, Wimo et al. and Costa et al. demonstrated that this approach might be cost-effective.[15,16] Therefore, future research should consider longer time horizons to demonstrate potential cost savings. An example of a sector with potential cost savings is long-term care. The aforementioned results by Neubert et al. highlight the costs that could be saved through the preservation of functional independence.[30] Interventions that aim to stabilize the level of functioning and foster resilience might be the key to reducing and postponing these costs long term.

3.2 | Limitations

Generally the coronavirus disease 2019 (COVID-19) pandemic may have influenced our study. For example, patients in the intervention group more frequently reported a negative impact of restrictions on nutrition.[11] As this has been an active component of the intervention, the effect of the intervention might have been limited. However, after adjustment there was no evidence of a group-specific impact.[11] Given that specific dietary changes were not assessed, this observation cannot be fully explained. Concerning access to health care, we cannot rule out that measures as preventive approaches have been postponed. There are further challenges originating from the characteristics of the study. At baseline, 1030 participants were included, but due to attrition the analytical sample consisted of 819 participants. After consideration, the primary investigators of the study decided not to consider these participants. To keep our results comparable, we used the same sample as the effectiveness evaluation.[11] In addition, the use of questionnaires completed by participants is associated with risk of bias. Self-reporting of outpatient and inpatient service utilization correlates with the officially documented use, but heavy use of services tends to be underreported. Hence, we present conservative estimates.[31,32] Furthermore, the assessment of informal care can only be conducted by asking/observing caregiver or recipient. A validation of our measurement is not possible as there is no official documentation. Furthermore, there are no studies that examine the validity of the FIMA with regard to the measurement of informal care, as is the case for the Resource Utilization in Dementia (RUD) instrument.[33,34] Finally, there has been no documentation about the exact duration of interventional visits and telephone contacts. Therefore, the calculation of intervention costs is based on standard assumptions about the duration and does not reflect actual resource/time utilization.

The main limitation is the time horizon of 24 months. This limitation is twofold. On the one hand, we assessed follow-up data only after 24 months by a recall period of 4 months. The limitation is that we had to calculate 24-month costs by multiplying the 4 months cost by 6. Therefore, we have lost information on the course of resource utilization over the 2-year period. To gain insight into the possible effect, we can use the result by a study by Costa et al. based on MAPT[16] over 36 months. The authors found that the 6-month costs per group remained quite stable over the course of the first 24 months. Therefore, our approach might not result in a major bias. However, as the intervention in AgeWell.de consisted of more components but was less intensive than MAPT, this should be viewed with caution. On the other hand, in our sample, the mean age was 69 years at baseline. After 2 years and with an average age of 71 years, it is not to be expected that there will be recognizable effects on functional decline. Nevertheless, the information on early trends in resource utilization, the short-term differences in the development of direct-rated HRQOL, as well as the specific role of depression and the results in the female subsample, are valuable information for stakeholders in the field of primary prevention, for example, to support them in the political decision-making process or in specifying future long-term modeling studies.

4 | CONCLUSIONS

Our evaluation presents evidence that the intervention is cost-effective, especially in the female subgroup. However, this conclusion is subject to a decision on the WTP and the influence of limiting factors such as the time horizon.

ACKNOWLEDGMENTS

AgeWell.de is funded by the German Federal Ministry for Education and Research (BMBF; reference numbers: 01GL1704A, 01GL1704B, 01GL1704C, 01GL1704D, 01GL1704E, 01GL1704F). The BMBF had no role in the design of this study and had no role during its execution, analyses, interpretation of the data, writing of the present paper, or decision to submit results.

Members of the AGEWELL.DE study group

Principal Investigator and Co-Principal Investigators: Steffi G. Riedel-Heller (PI), Wolfgang Hoffmann, Jochen Gensichen, Walter E. Haefeli, Hanna Kaduszkiewicz, Hans-Helmut König, Thomas Frese, David Czock, Jochen René Thyrian, Birgitt Wiese.

Franziska Berg, Andrea Bischhoff, Christian Brettschneider; Mandy Claus, Juliane Döhring, Alexander Eßer, Corinna Gräble, Caroline Jung-Sievers, Kerstin Klauer-Tiedtke, Kerstin Krebs-Hein, Sebastian Lange, Paula Liegert, Dagmar Lochmann, Tobias Luck, Melanie Luppa, Silke Mamone, Andreas Meid, Michael Metzner, Lydia Neubert, Anke Oey, Susanne Röhr, Franziska-Antonia Zora Samos, Karin Schumacher, Hanna Seidling, Theresa Terstegen, Sandy Thieme, Lars Wamsiedler, Tanja Wehran, Marina Weißenborn, Flora Wendel, Ines Winkler, Isabel Zöllinger, Andrea Zülke, and Ina Zwingmann. Furthermore, the authors want to thank all participating GPs and study participants of the AgeWell.de trial for their cooperation.

Open access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST STATEMENT

The authors confirm that there are no conflicts of interest.

INSTITUTIONAL REVIEW BOARD STATEMENT

The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee at the Medical Faculty of the University of Leipzig (protocol code BB 369/17-ek) and at all participating study centers.

INFORMED CONSENT STATEMENT

All study subjects gave written informed consent at their respective GP practices prior to participation.

TRIAL REGISTRATION

AgeWell.de is registered in the German Clinical Trials Register (DRKS; registration number: DRKS00013555).

ORCID

Christian Brettschneider https://orcid.org/0000-0002-5280-1075

REFERENCES

1. Nichols E, Steinmetz JD, Vollset SE, et al. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *Lancet Public Health*. 2022;7:e105-e125.
2. Wimo A, Guerchet M, Ali G-C, et al. The worldwide costs of dementia 2015 and comparisons with 2010. *Alzheimers Dement*. 2017;13:1-7.
3. Wimo A, Jönsson L, Bond J, Prince M, Winblad B. The worldwide economic impact of dementia 2010. *Alzheimers Dement*. 2013;9:1-11.e3.
4. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. 2020;396:413-446.
5. Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet*. 2015;385:2255-63.
6. Kivipelto M, Solomon A, Ahtiluoto S, et al. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER): study design and progress. *Alzheimers Dement*. 2013;9:657-665. doi:10.1016/j.jalz.2012.09.012
7. den Brok MGHE, Hoevenaar-Blom MP, Coley N, et al. The effect of multidomain interventions on global cognition, symptoms of depression and apathy — a pooled analysis of two randomized controlled trials. *J Prev Alzheimers Dis*. 2022;9(1):96-103. doi:10.14283/jpad.2021.53
8. Chen L-K, Hwang A-C, Lee W-J, et al.; Taiwan Health Promotion Intervention Study for Elders research group. Efficacy of multidomain interventions to improve physical frailty, depression and cognition: data from cluster-randomized controlled trials. *J Cachexia Sarcopenia Muscle*. 2020;11(3):650-662. doi:10.1002/jcsm.12534
9. Andrieu S, Guyonnet S, Coley N, et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. *Lancet Neurol*. 2017;16(5):377-389. doi:10.1016/S1474-4422(17)30040-6
10. Zülke A, Luck T, Pabst A, et al. AgeWell.de—study protocol of a pragmatic multi-center cluster-randomized controlled prevention trial against cognitive decline in older primary care patients. *BMC Geriatr*. 2019;19(1):203. doi:10.1186/s12877-019-1212-1
11. Zülke AE, Pabst A, Luppa M, et al. A multidomain intervention against cognitive decline in an at-risk-population in Germany: results from the cluster-randomized AgeWell.de trial. *Alzheimers Dement*. 2023;20:615-628. doi:10.1002/alz.13486
12. Zülke AE, Pabst A, Luppa M, et al. Effects of a multidomain intervention against cognitive decline on dementia risk profiles — results from the AgeWell.de trial. *Alzheimers Dement*. 2024;20(8):5684-5694. doi:10.1002/alz.14097
13. Kato G, Doi T, Arai H, Shimada H. Cost-effectiveness analysis of combined physical and cognitive exercises programs designed for preventing dementia among community-dwelling healthy young-old adults. *Phys Ther Res*. 2022;25(2):56-67. doi:10.1298/ptr.E10153
14. Zhang Y, Kivipelto M, Solomon A, Wimo A. Cost-effectiveness of a health intervention program with risk reductions for getting demented: results of a Markov Model in a Swedish/Finnish setting. *J Alzheimers Dis*. 2011;26:735-744. doi:10.3233/JAD-2011-110065
15. Wimo A, Handels R, Antikainen R, et al. Dementia prevention: The potential long-term cost-effectiveness of the FINGER prevention program. *Alzheimers Dement*. 2022;19:999-1008. doi:10.1002/alz.12698
16. Costa N, Mounié M, Pagès A, et al. The cost-effectiveness of three prevention strategies in Alzheimer's disease: results from the Multidomain Alzheimer Preventive Trial (MAPT). *J Prev Alzheimers Dis*. 2021;8(4):425-435. doi:10.14283/jpad.2021.47
17. Kivipelto M, Ngandu T, Laatikainen T, Winblad B, Soininen H, Tuomilehto J. Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. *Lancet Neurol*. 2006;5:735-41. doi:10.1016/s1474-4422(06)70537-3
18. Röhr S, Zülke A, Luppa M, et al. Recruitment and baseline characteristics of participants in the AgeWell.de Study-a pragmatic cluster-randomized controlled lifestyle trial against cognitive decline. *Int J Environ Res Public Health*. 2021;18(2). doi:10.3390/ijerph18020408
19. EuroQol Group. EuroQol–a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16:199-208. doi:10.1016/0168-8510(90)90421-9
20. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011;20:1727-1736. doi:10.1007/s11136-011-9903-x
21. Seidl H, Bowles D, Bock JO, et al. [FIMA–questionnaire for health-related resource use in an elderly population: development and pilot study]. *Gesundheitswesen*. 2015;77(1):46-52. FIMA–Fragebogen zur Erhebung von Gesundheitsleistungen im Alter: Entwicklung und Pilotstudie. doi:10.1055/s-0034-1372618
22. Bock JO, Brettschneider C, Seidl H, et al. Ermittlung standardisierter Bewertungssätze aus gesellschaftlicher Perspektive für die gesundheitsökonomische Evaluation. SCORING: Zeitschriftenaufsätze. *Gesundheitswesen*. 2015;77(1):53-61. doi:10.1055/s-0034-1374621
23. Rote Liste Service GmbH. Rote Liste. Rote Liste Service GmbH. 2018. Frankfurt/Main: Rote Liste Service GmbH; 2018.
24. German Federal Statistical Office. Verdienste und Arbeitskosten. Wiesbaden: German Federal Statistical Office; 2018.
25. German Federal Statistical Office. Verbraucherpreise [Consumer Prices]. Wiesbaden: German Federal Statistical Office. Accessed June 22, 2022. https://www.destatis.de/DE/ZahlenFakten/GesamtwirtschaftUmwelt/Preise/Verbraucherpreisindizes/Tabellen_/VerbraucherpreiseKategorien.html;jsessionid=014AA97F7BFDDE
26. Azur MJ, Stuart EA, Frangakis C, Leaf PJ. Multiple imputation by chained equations: what is it and how does it work?. *Int J Methods Psychiatr Res*. 2011;20(1):40-49. doi:10.1002/mpr.329
27. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med*. 2011;30:377-399. doi:10.1002/sim.4067
28. Hoch JS, Briggs AH, Willan AR. Something old, something new, something borrowed, something blue: a framework for the marriage of health econometrics and cost-effectiveness analysis. *Health Econ*. 2002;11(5):415-430. doi:10.1002/hec.678
29. Briggs AH, O'Brien BJ, Blackhouse G. Thinking outside the box: recent advances in the analysis and presentation of uncertainty in cost-effectiveness studies. *Annu Rev Public Health*. 2002;23:377-401.
30. Neubert L, König H-H, Löbner M, et al. Excess costs of dementia in old age (85+) in Germany: results from the AgeCoDe-AgeQualiDe study. *J Econ of Ageing*. 2021;20:100346. doi:10.1016/j.jeoa.2021.100346
31. Reijneveld SA, Stronks K. The validity of self-reported use of health care across socioeconomic strata: a comparison of survey and registration data. *Int J of Epidemiol*. 2001;30:1407-1414. doi:10.1093/ije/30.6.1407
32. Ritter PL, Stewart AL, Kaymaz H, Sobel DS, Block DA, Lorig KR. Self-reports of health care utilization compared to provider records. *Jour-*

nal of Clinical Epidemiology. 2001;54(2):136-141. doi:10.1016/S0895-4356(00)00261-4

33. Neubauer S, Holle R, Menn P, Gräßel E. A valid instrument for measuring informal care time for people with dementia. *Int J Geriatr Psychiatry*. 2009;24(3):275-282. doi:10.1002/gps.2103
34. Wimo A, Jonsson L, Zbrozek A. The resource utilization in dementia (RUD) instrument is valid for assessing informal care time in community-living patients with dementia. *J Nutr Health Aging*. 2010;14(8):685-690. doi:10.1007/s12603-010-0316-2

SUPPORTING INFORMATION

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

How to cite this article: Brettschneider C, Buczak-Stec E, Luppa M, et al. Cost-effectiveness of a multicomponent intervention against cognitive decline. *Alzheimer's Dement*. 2025;11:e70028. https://doi.org/10.1002/trc2.70028