Received: 17 July 2024 | Revised: 21 October 2024 | Accepted: 22 November 2024

DOI: 10.1002/dad2.70050

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

RESEARCH ARTICLE

Modifiable risk factors and symptom progression in dementia over up to 8 years—Results of the DelpHi-MV trial

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Funding information
Alzheimer Forschung Initiative

Abstract

INTRODUCTION: This study investigated the association between modifiable factors and symptom progression in dementia over up to 8 years.

METHODS: Multilevel growth curve models assessed the role of modifiable risk factors (low education, hearing impairment and its treatment, depression, physical inactivity, diabetes and its treatment, smoking, hypertension and its treatment, obesity, alcohol consumption, social isolation, and visual impairment) on cognitive and functional trajectories in 353 people with dementia.

RESULTS: Higher education was associated with higher initial cognitive status but faster decline. Antidiabetic medication was associated with slower cognitive decline, whereas depression and visual impairment were linked to low baseline functioning and faster cognitive decline.

DISCUSSION: Several modifiable risk factors influenced symptom progression. Education initially had a protective effect, whereas depressive symptoms were linked to worse symptom progression. Treatment of comorbidities (diabetes, visual impairment) could have a positive impact on dementia symptoms. Modifiable risk factors are promising targets for tertiary prevention.

KEYWORDS
activities of daily living, Alzheimer Disease, anti-diabetic medication, cognition, cognitive decline, comorbidities, depressive symptoms, education, functional decline, lifestyle, medication, visual impairment

Highlights

- Modifiable risk factors were associated with symptom progression in dementia over up to 8 years.
- More education was associated with higher initial cognitive status but faster decline.
- Depressive symptoms were linked to less favorable symptom progression.
- Treatment of comorbidities (diabetes, visual impairment) may positively impact the course of symptoms.
- Modifiable risk factors are promising targets for tertiary prevention.

1 | BACKGROUND

With the global phenomenon of population aging,[1] the number of people with Alzheimer's disease and related dementias (ADRD) is increasing worldwide.[2,3] A promising approach to curb the sharply rising numbers is through preventive measures.[4–6] Although our knowledge about modifiable risk factors for the development of dementia continues to grow,[7] we still know little about how they influence the course of ADRD.[8] However, this knowledge is crucial for identifying possible strategies for tertiary prevention, specifically interventions that can potentially delay symptom progression.

1.1 | Modifiable dementia risk factors

There are dementia risk factors, such as age or genetic risk factors (e.g., Apolipoprotein E [*APOE*] 4ε), which are non-modifiable. At the same time, evidence is growing regarding modifiable dementia risk factors across the lifespan. The *Lancet Commission for Dementia Prevention, Intervention, and Care* summarized evidence for a total of 14 modifiable risk factors for ADRD, including less education, hearing impairment, high low-density lipoprotein (LDL) cholesterol, depression, traumatic brain injury, physical inactivity, diabetes, smoking, hypertension, obesity, excessive alcohol consumption, social isolation, air pollution, and visual impairment.[4,6] There are several mechanisms through which these modifiable factors may influence dementia risk: they can affect the development and maintenance of cognitive reserve (e.g., through education and social contact), promote neuropathological developments and vascular damage, or foster stress and inflammation (e.g., through smoking, alcohol consumption, and hypertension).[5,6]

1.2 | Progression of dementia symptoms

The main symptoms of ADRD are cognitive and functional decline. However, the course of symptoms is highly variable and differs greatly between individuals.[8–10] Risk factors for the development of ADRD have been studied extensively, whereas our knowledge about risk and protective factors for symptom progression is limited. There is initial evidence suggesting that younger individuals, men, individuals with fewer neuropsychiatric symptoms, and individuals with a higher cognitive and functional status, as well as a lower burden of comorbidities, show a slower decline.[10–13] Gains in knowledge about the role of modifiable factors in the progression of ADRD are important for the development of future interventions for tertiary prevention.

However, current research findings are heterogeneous, and the studies that address the question of protective and risk factors for the progression of dementia symptoms often have significant limitations: they are often cross-sectional or investigate only a few risk factors, such as vascular risk factors or multimorbidity over short periods of 1 or 2 years. Furthermore, the effect of the presence of treatment of modifiable risk factors on the course of symptoms, such as hearing aids for hearing impairment or anti-diabetic drugs for diabetes, has rarely been studied.

1.3 | The present study

There is a lack of studies examining the role of a variety of modifiable factors for the progression of dementia symptoms over an extended timeframe. Thus the aim of the present study was to investigate the role of a broad range of modifiable factors and, where available, their treatment, on the course of ADRD over a period of up to 8 years. For this purpose, data from a cohort of community-dwelling individuals who screened positive for dementia in primary care were utilized.

2 | METHODS

2.1 | Data and study sample

Data from the cluster-randomized-controlled DelpHi-MV trial (dementia: life- and person-centered help in Mecklenburg-Western Pomerania, Germany) were used.[14,15] The trial was designed to test the effectiveness of dementia care management (DCM) compared to care as usual (CAU) over a period of 12 months[15] (clinicaltrials.gov identifier: NCT01401582). In the intervention, specially trained nurses visited people in their homes who screened positive for dementia and provided individualized support for the management and coordination of care. Further details about the intervention can be found elsewhere.[14] After completion of the trial, the sample was followed as a prospective cohort study for a total of 8 years.

In 125 participating general practitioners' (GP) practices, 6838 patients were screened for eligibility. Of these, 1166 screened positive for dementia (DemTect score <9) and also met the other inclusion criteria (age 70+, living at home). A total of 634 gave their informed consent to participate in the trial. The trial received ethical approval from the Chamber of Physicians of Mecklenburg-Western Pomerania—registry number: BB 20/11. The baseline assessment took place between April 2012 and May 2015. At baseline, participants were visited twice in their homes and interviewed in a comprehensive, standardized, computerized face-to-face interview. After baseline, they were visited annually by specially qualified nurses, during which their cognitive status was assessed and they were interviewed about further symptoms. In addition to the extensive information from the interviews, patient records, including diagnoses with International Classification of Diseases (ICD) codes and medications with anatomical therapeutic chemical / defined daily dose classification (ATC) codes, were collected. The current analysis is based on a study sample of 353 individuals with at least two assessments of cognitive performance and daily functioning available over a follow-up period of up to 8 years. Figure S1 in the supplementary material shows the participant flow over 8 years.

2.2 | Measures

2.2.1 | Primary outcomes: cognitive and functional status

Cognitive status was assessed annually using the Mini-Mental State Examination (MMSE),[16] covering abilities like orientation, recall, attention, and calculation. A total score ranging between 0 and 30 can be achieved. Scores of 27 and above indicate normal cognitive performance, scores between 20 and 26 suggest mild cognitive impairment, scores between 10 and 19 indicate moderate dementia, and scores below 10 reflect severe dementia.

Functional status was assessed annually using the Bayer Activities of Daily Living scale (B-ADL).[17] The B-ADL comprises a total of 25 items related to daily problems (e.g., personal care, shopping, meal preparation). Overall scores range from 1 to 10; the data were recoded so that higher scores indicated higher everyday function.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors used PubMed to review the literature. Few studies investigated the role of modifiable dementia risk factors on symptom progression; these are presented in the introduction.
2. **Interpretation**: The longitudinal analysis showed that some modifiable risk factors were associated with symptom progression in dementia. Education initially had a protective effect, which reversed over time. The treatment of comorbidities (diabetes, visual impairment) could have a positive impact on symptom progression. Depressive symptoms were associated with a less favorable symptom course.
3. **Future directions**: Modifiable risk factors are promising targets for tertiary prevention and should be further investigated in intervention trials.

2.2.2 | Modifiable risk factors

At baseline, *educational attainment* was recorded and converted into the classification according to the International Standard Classification of Education (ISCED).[18] Level 1 ("low education") corresponds to primary, level 2 ("moderate education") to lower secondary, and level 3 ("high education") to upper secondary education.

Self-reported *hearing impairment* at baseline was assessed using the Standardized Assessment of Elderly People in Primary Care (STEP).[19] The participants were asked (Q1) whether they had difficulties following a conversation due to hearing problems, (Q2) whether they owned and (Q3) used a hearing aid, and (Q4) were able to hear sufficiently with the hearing aid. The participants were divided into three groups: (1) people with sufficient hearing capabilities (no to Q1 and Q2); (2) people with limited, but compensated hearing capabilities (yes to Q1, Q2, Q3, and Q4); and (3) people with limited hearing capabilities (yes to Q1; no to Q2, Q3, or Q4).

Depressive symptoms were assessed at baseline using the Geriatric Depression Scale (GDS) [20] with a score range of 0 to 15 points, with more than 5 points indicating mild to moderate depression and more than 10 points indicating severe depression.

Physical activity at baseline was assessed using the STEP questionnaire,[19] with a list of eight physical activities (e.g., cycling, walking, swimming). Three groups were formed: People who engaged in none, one, or at least two physical activities.

The presence of *diabetes* was defined as having an ICD-10 diagnosis (E10-E14, G63.2, H36.0, N08.3) or using anti-diabetic medication.[21] The anti-diabetic medication included insulin: A10A, and other glucose-lowering medications: A10B.

Smoking behavior at baseline was assessed using the STEP questionnaire.[19] People were asked whether they smoked cigarettes, cigars, or pipes, or chewed or snuffed tobacco (answer options: never, used to, yes).

The presence of *hypertension* was defined as an ICD-10 (Tenth Revision) diagnosis of high blood pressure (I10-I15) or the use of at least two anti-hypertensive medications from two different drug groups.[22] The anti-hypertensive medications included were: antihypertensive drugs, C02; vasodilators, C04; β-blockers, C07; calcium channel blockers, C08; renin–angiotensin system inhibitors, C09; and diuretics, C03.

Clinically relevant *obesity* was defined using the ICD-10 diagnosis.

Self-reported *alcohol consumption* at baseline was assessed using the STEP questionnaire,[19] which asked whether the person currently drinks alcohol (response option: no, yes—less than daily, yes—daily).

Social support was assessed using the FSozU K-22 ("Questionnaire for the assessment of social support").[23] The 22-item questionnaire assesses perceived social support from family, friends, and acquaintances. The scale ranged from 1 to 5, with higher values indicating greater social support. The overall score was calculated as the mean.

Visual impairment at baseline was assessed with two items from the STEP questionnaire,[19] asking whether the person had difficulty reading newspapers or seeing people on the street (yes or no). Visual impairment was present if the person answered yes to at least one of the items.

2.2.3 | Covariates

Socio-demographic information like age, sex, and whether the person lived alone was recorded at baseline.

Group allocation (DCM vs CAU) was included as a covariate because the study began as a randomized controlled trial.

2.3 | Statistical analysis

Data processing and all statistical analyses were conducted using R.[24] The significance level was set at $p < 0.05$. In order to investigate the role of modifiable factors on cognitive and functional status

over 8 years, multilevel growth curve models were calculated using the *lme4* package.[25] The nested structure of the data in clusters of treating GPs was taken into account using a random intercept. The models were built systematically, starting from the null model. Random intercepts (for the individual and the GP) and random slopes for the time variable and linear and polynomial time variables (second and third degree) were gradually included in the model and the model fit (akaike information criterion (AIC), bayesian information criterion (BIC)) was compared. In the next step, the predictors and their interactions with the time variables were included in the model. Interactions with $p > 0.10$ were identified as potentially poor fitting. We used the likelihood ratio test to compare the model with and without the interaction; if the fit was significantly better with the interaction, we retained the more complex model. Thus nonsignificant interactions could remain in the model if they significantly improved model fit.

3 | RESULTS

3.1 | Descriptive statistics

Table 1 provides an overview of the descriptive statistics at baseline. Participants had a mean age of 80.3 years (SD = 5.3), the majority were female (59.8%), and about half lived alone (49.9%). The mean cognitive status at baseline was in the range of mild dementia (MMSE score of 23.0 [SD = 4.6]). The mean functional status at baseline, measured using the B-ADL scale, was 7.5 (SD = 2.4).

3.2 | Prediction of cognitive status over 8 years

For modeling cognitive status over time, the multilevel growth curve model with a linear time variable, random intercepts (for the individual and the GP), and a random slope showed the best fit. Figure 1 shows the mean predicted trajectory over 8 years. The MMSE score decreased on average by 1.5 points per year. Table 2 displays the parameter estimates for the null model (Model 1).

The model with covariates and modifiable risk factors (Table 2, Model 2) showed a significant main effect for the covariate sex; women had a lower cognitive status at the beginning of the study than men ($b = 1.21$, $p < 0.043$). Individuals with moderate education had a higher cognitive status at the beginning of the study than those with low education ($b = 1.39$, $p = 0.034$).

The rate of cognitive decline, however, was faster in individuals with moderate compared to low education ($b = -0.58$, $p = 0.026$). In addition, cognitive decline was more pronounced in people with depression ($b = -0.68$, $p = 0.025$) and in people with visual impairment ($b = -0.48$, $p = 0.018$). Finally, people with diabetes showed a slower cognitive decline over time ($b = 0.56$, $p = 0.006$). For the remaining covariates and modifiable risk factors, we found no significant association with cognitive status or rate of cognitive decline.

In the model that accounted for the treatment of risk factors (Table 2, Model 3), we observed results similar to those of Model 2.

TABLE 1 Description of participant characteristics at baseline.

Variable	Total sample ($n = 353$)
Sociodemographic variables	
Age in years, mean (SD)	80.3 (5.3)
Sex	
Female, *n* (%)	211 (59.8)
Living situation	
Alone living, *n* (%)	176 (49.9)
Group allocation	
Intervention group, *n* (%)	252 (71.4)
Outcomes	
Cognitive status, mean (SD)	23.0 (4.6)
Functional status, mean (SD)	7.5 (2.4)
Potentially modifiable risk factors	
Education, *n* (%)	
Low, *n* (%)	62 (17.7)
Moderate, *n* (%)	276 (78.6)
High, *n* (%)	13 (3.7)
Hearing impairment	
None, *n* (%)	194 (55.1)
Uncompensated, *n* (%)	90 (25.6)
Compensated, *n* (%)	68 (19.3)
Depression, *n* (%)	51 (14.5)
Physical activity	
None, *n* (%)	57 (16.1)
One activity, *n* (%)	129 (36.5)
Two and more activities	167 (47.3)
Diabetes	
None, *n* (%)	177 (50.1)
Uncompensated, *n* (%)	72 (20.4)
Compensated, *n* (%)	104 (29.5)
Smoking	
Nonsmoker, *n* (%)	201 (56.9)
Used to, *n* (%)	134 (38.0)
Yes, *n* (%)	18 (0.1)
Hypertension	
None, *n* (%)	53 (15.0)
Uncompensated, *n* (%)	14 (4.0)
Compensated, *n* (%)	286 (81.0)
Obesity, *n* (%)	41 (11.6)
Alcohol consumption	
None, *n* (%)	154 (43.6)
Less than daily, *n* (%)	174 (49.3)
Daily, *n* (%)	25 (0.07)
Social support, mean (SD)	4.1 (0.6)
Visual impairment, *n* (%)	155 (44.7)

Abbreviation: SD, standard deviation.

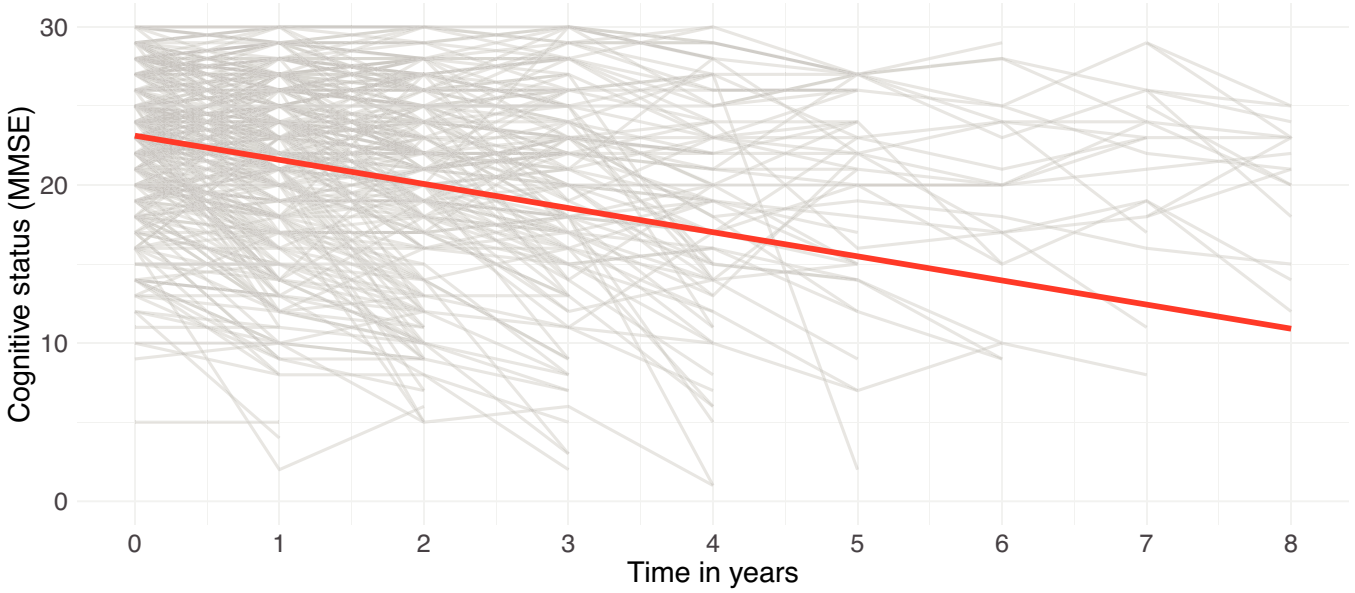

FIGURE 1 Cognitive trajectories across 8 years. Mean predicted trajectory for the whole sample in red; observed individual trajectories for 100 randomly selected individuals in gray.

However, we found a significantly slower cognitive decline in people receiving anti-diabetic medications ($b = 0.66$, $p = 0.005$). We found no significant association of compensated hearing impairment or anti-hypertensive medications with cognitive status or the rate of decline.

3.3 | Prediction of functional status over 8 years

For modeling functioning in activities of daily living, the multilevel growth curve model with linear and quadratic time variables, random intercepts, and random slope showed the best fit. Figure 2 shows the mean predicted trajectory over 8 years. The B-ADL score decreased on average by 1 point per year, with this effect slowing down over time. Table 3 displays the parameter estimates for the null model (Model 4).

In the model with covariates and modifiable risk factors (Table 3, Model 5), there was a negative main effect for the covariate age; people of older age had a lower everyday function at baseline than younger people ($b = -0.08$, $p = 0.001$). Among the modifiable factors, we found that people with depression had a lower level of daily functioning ($b = -1.17$, $p = 0.001$) and that people who were physically active showed a higher level of daily functioning at baseline ($b = 1.27$, $p = 0.001$ for one physical activity; $b = 1.45$, $p < 0.001$ for two or more physical activities). People with visual impairment showed lower everyday function ($b = -0.72$, $p = 0.004$). For the other covariates and modifiable risk factors, we found no significant association with everyday function. None of the variables considered significantly predicted the rate of functional decline.

The model where treatment of risk factors was accounted for (Table 3, Model 6) showed results similar to those of Model 5. In addition, individuals with compensated hearing impairment had a significantly higher functional status at baseline ($b = 0.79$, $p = 0.014$) than those who reported no hearing impairment. We found no significant association of anti-hypertensive or anti-diabetic medications with everyday function.

4 | DISCUSSION

In our longitudinal study, several modifiable dementia risk factors were associated with rates of progression of cognitive and functional decline. Specifically, we found associations between educational level, depressive symptoms, visual impairment, and treated diabetes with symptom progression over a period of up to 8 years.

Education seemed to be a protective factor for cognitive impairment in the beginning, but a risk factor for a more dynamic cognitive decline later. This finding is consistent with the effect and trajectory expected from the phenomenon of cognitive reserve. In people with more education, the first symptoms of dementia appear later—despite advanced neuropathology—because the brain can successfully compensate for a longer period due to the built-up cognitive reserve. However, if the pathology reaches a level of severity at which compensation is no longer successful, the symptoms then progress at a faster rate and eventually reach the same level as in people with less cognitive reserve.[26,27]

Regarding depression or depressive symptoms, our results are in line with previous research indicating that depressive symptoms not only increase the risk of dementia [28] and impair daily functioning,[29] but can also accelerate the progression of dementia symptoms in people with pre-existing dementia.[30] Depressive symptoms were associated with both faster cognitive decline over the 8-year study period and reduced daily functioning at the beginning of the study period. This

TABLE 2 Prediction of cognitive status across 8 years.

Model 1. Null model	Estimate	95% CI (lower)	95% CI (upper)	*p*	
Fixed effects					
Intercept	23.12	22.64	23.60	**<0.001**	***
Time	−1.53	−1.73	−1.32	**<0.001**	***
Random effects					
Intercept (person)	16.68				
Time	2.34				
Intercept (person)×time	0.42				
Intercept (GP)	0.03				
Residual	6.30				
ICC	0.89				
Marginal R^2/conditional R^2	0.154/0.906				
Model 2. Modifiable risk factors	**Estimate**	**95% CI (lower)**	**95% CI (upper)**	***p***	
Fixed effects					
Intercept	19.99	11.07	28.92	**<0.001**	***
Time	−1.41	−2.17	−0.64	**<0.001**	***
Sociodemographic variables					
Age	0.00	−0.10	0.10	0.987	
Sex (ref: male)	−1.21	−2.38	−0.04	**0.043**	*
Living situation (ref: cohabitating)	0.31	−0.70	1.33	0.545	
Group allocation (ref: CAU)	−0.02	−1.17	1.13	0.973	
Potentially modifiable risk factors					
Education (ref: low)					
Moderate	1.39	0.10	2.67	**0.034**	*
High	0.96	−1.77	3.70	0.489	
Time×moderate education	−0.58	−1.10	−0.07	**0.026**	*
Time×high education	−0.99	−2.19	0.21	0.107	
Hearing impairment (ref: none)	1.00	−0.10	2.09	0.074	
Depression (ref: none)	0.43	−1.01	1.87	0.559	
Time×depression	−0.68	−1.27	−0.08	**0.025**	*
Physical activity (ref: none)					
One activity	1.08	−0.37	2.54	0.145	
Two and more activities	0.78	−0.66	2.23	0.288	
Diabetes (ref: none)	0.02	−0.96	0.99	0.973	
Time×diabetes	0.56	0.16	0.96	**0.006**	**
Smoking (ref: nonsmoker)					
Used to	−0.36	−1.48	0.75	0.525	
Yes	0.83	−1.35	3.01	0.455	
Hypertension (ref: none)	0.88	−0.50	2.27	0.211	
Time×hypertension	0.52	−0.08	1.12	0.091	
Obesity (ref: none)	0.19	−1.34	1.71	0.811	
Alcohol consumption (ref: none)					
Less than daily	0.61	−0.39	1.61	0.234	
Daily	−0.36	−2.29	1.58	0.718	
Social support	0.16	−0.70	1.02	0.711	
Visual impairment (ref: none)	−0.04	−1.02	0.95	0.942	

(Continues)

TABLE 2 (Continued)

Model 2. Modifiable risk factors	Estimate	95% CI (lower)	95% CI (upper)	*p*	
Time×visual impairment	−0.48	−0.89	−0.08	**0.018**	*
Random effects					
Intercept (person)	14.66				
Time	2.01				
Intercept (person)×time	0.45				
Intercept (GP)	0.58				
Residual	6.24				
ICC	0.88				
Marginal R^2/conditional R^2	0.189/0.902				
Model 3. Modifiable risk factors with treatment	**Estimate**	**95% CI (lower)**	**95% CI (upper)**	***p***	
Fixed effects					
Intercept	20.78	11.84	29.72	**<0.001**	***
Time	−1.44	−2.21	−0.67	**<0.001**	***
Sociodemographic variables					
Age	−0.01	−0.11	0.09	0.850	
Sex (ref: male)	−1.02	−2.20	0.15	0.088	
Living situation (ref: cohabitating)	0.19	−0.82	1.20	0.709	
Group allocation (ref: CAU)	0.23	−0.92	1.37	0.698	
Potentially modifiable risk factors					
Education (ref: low)					
Moderate	1.58	0.30	2.86	**0.016**	*
High	1.22	−1.51	3.95	0.381	
Time×moderate	−0.55	−1.07	−0.04	**0.036**	*
Time×high	−0.96	−2.17	0.26	0.122	
Hearing impairment (ref: none)					
Uncompensated	0.98	−0.16	2.13	0.092	
Compensated	0.48	−0.79	1.74	0.461	
Depression (ref: none)	0.48	−0.96	1.91	0.517	
Time×depression	−0.64	−1.24	−0.04	**0.038**	*
Physical activity (ref: none)					
One activity	0.87	−0.59	2.33	0.245	
Two and more activities	0.68	−0.77	2.12	0.358	
Diabetes (ref: none)					
Uncompensated	−0.66	−1.93	0.60	0.305	
Compensated	0.61	−0.52	1.73	0.292	
Time×uncompensated	0.45	−0.09	0.99	0.101	
Time×compensated	0.66	0.20	1.12	**0.005**	**
Smoking (ref: nonsmoker)					
Used to	−0.30	−1.41	0.81	0.598	
Yes	1.19	−0.99	3.37	0.283	
Hypertension (ref: none)					
Uncompensated	−1.39	−4.13	1.36	0.321	
Compensated	1.09	−0.29	2.47	0.123	
Time×uncompensated	0.14	−1.15	1.43	0.834	
Time×compensated	0.54	−0.06	1.15	0.078	

(Continues)

TABLE 2 (Continued)

Model 3. Modifiable risk factors with treatment	Estimate	95% CI (lower)	95% CI (upper)	*p*	
Obesity (ref: none)	0.07	−1.45	1.58	0.931	
Alcohol consumption (ref: none)					
Less than daily	0.54	−0.46	1.55	0.290	
Daily	−0.04	−1.98	1.90	0.965	
Social support	0.06	−0.79	0.92	0.885	
Visual impairment (ref: none)	−0.11	−1.09	0.87	0.826	
Time×visual impairment	−0.50	−0.90	0.10	**0.016**	*
Random effects					
Intercept (person)	14.36				
Time	2.03				
Intercept (person)×time	0.44				
Intercept (GP)	0.53				
Residual	6.23				
ICC	0.88				
Marginal R^2/conditional R^2	0.193/0.901				

Abbreviations: CI, confidence interval, CAU, care as usual, GP, general practitioner.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

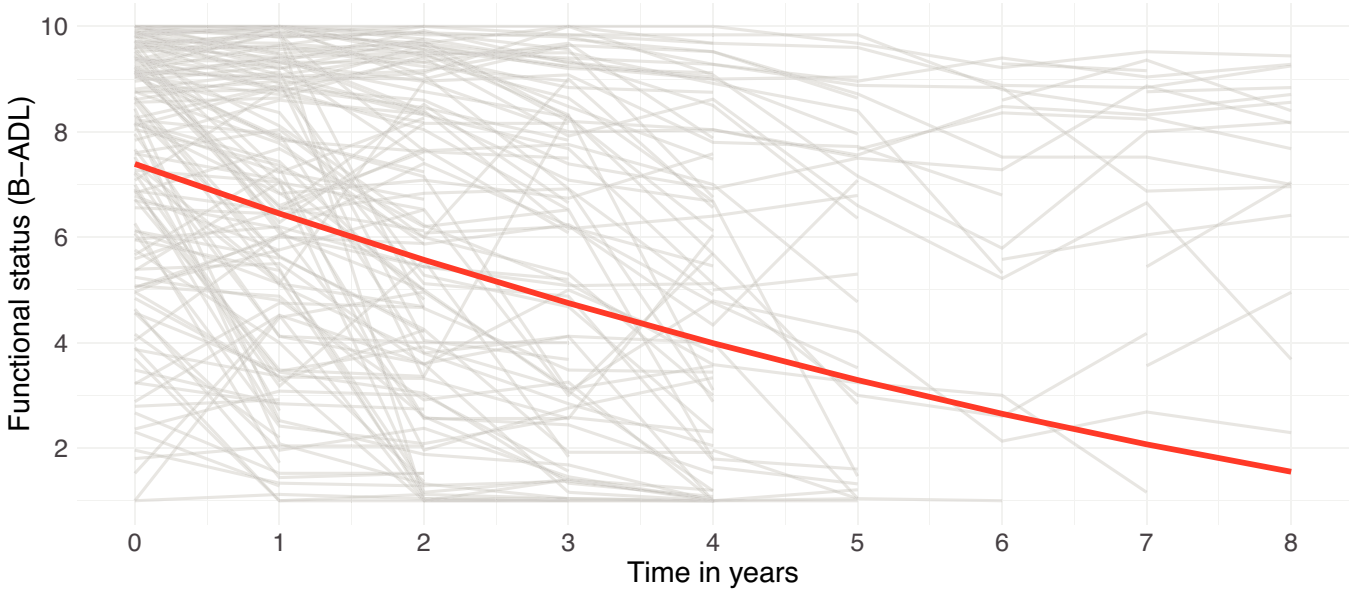

FIGURE 2 Trajectories in daily functioning across 8 years. Mean predicted trajectory for the whole sample in red; observed individual trajectories for 100 randomly selected individuals in gray.

suggests that depressive symptoms may not only be a possible starting point for primary and secondary prevention but also for tertiary prevention in pre-existing ADRD. However, it should be noted that the relationship between dementia symptoms and depression in pre-existing ADRD—as with the development of dementia—is not fully understood and may be bidirectional; for example, depressive symptoms may be a reaction to the decline in cognition and everyday function.[31]

Our study adds novel evidence about the potential role of visual impairment in the progression of dementia symptoms. We found reduced daily functioning at baseline and faster cognitive decline over time in people with visual impairment. This result is of special importance, since in many cases, visual impairment, like hearing impairment, is generally treatable at comparably low cost, and respective interventions (glasses, cataract surgery, hearing aids) are readily available in many health care systems. Indeed, there is already promising evidence

TABLE 3 Prediction of functional status across 8 years.

Model 4. Null model	Estimate	95% CI (lower)	95% CI (upper)	*p*	
Fixed effects					
Intercept	7.39	7.07	7.72	**<0.001**	***
Time	−0.97	−1.09	−0.86	**<0.001**	***
Time^2	0.03	0.02	0.05	**<0.001**	***
Random effects					
Intercept (person)	4.43				
Time	0.30				
Intercept (person)×time	0.11				
Intercept (GP)	0.57				
Residual	1.74				
ICC	0.83				
Marginal R^2/conditional R^2	0.195/0.862				
Model 5. Modifiable risk factors	**Estimate**	**95% CI (lower)**	**95% CI (upper)**	***p***	
Fixed effects					
Intercept	14.74	10.29	19.19	**<0.001**	***
Time	−0.82	−1.03	−0.60	**<0.001**	***
Time^2	0.03	0.02	0.05	**<0.001**	***
Sociodemographic variables					
Age	−0.08	−0.13	−0.04	**0.001**	**
Sex (ref: male)	−0.19	−0.77	0.39	0.528	
Living situation (ref: cohabitating)	0.14	−0.36	0.65	0.582	
Group allocation (ref: CAU)	−0.09	−0.72	0.53	0.769	
Potentially modifiable risk factors					
Education (ref: low)					
Moderate	−0.12	−0.76	0.52	0.708	
High	−1.35	−2.71	0.01	0.051	
Time×moderate education	−0.19	−0.40	0.02	0.082	
Time×high education	−0.47	−0.99	0.05	0.075	
Hearing impairment (ref: none)	0.24	−0.30	0.78	0.389	
Depression (ref: none)	−1.17	−1.87	−0.46	**0.001**	**
Physical activity (ref: none)					
One activity	1.27	0.55	1.99	**0.001**	**
Two and more activities	1.45	0.73	2.16	**<0.001**	***
Diabetes (ref: none)	0.26	−0.22	0.75	0.284	
Smoking (ref: nonsmoker)					
Used to	−0.19	−0.74	0.36	0.505	
Yes	1.00	−0.09	2.08	0.073	
Hypertension (ref: none)	0.25	−0.43	0.93	0.475	
Obesity (ref: none)	−0.07	−0.83	0.69	0.853	
Alcohol consumption (ref: none)					
Less than daily	0.35	−0.15	0.84	0.173	
Daily	0.00	−0.95	0.95	0.994	
Social support	−0.36	−0.79	0.07	0.099	
Visual impairment (ref: none)	−0.72	−1.20	−0.23	**0.004**	**

(Continues)

TABLE 3 (Continued)

Model 5. Modifiable risk factors	Estimate	95% CI (lower)	95% CI (upper)	*p*	
Random effects					
Intercept (person)	3.43				
Time	0.33				
Intercept (person)×time	0.11				
Intercept (GP)	0.38				
Residual	1.71				
ICC	0.81				
Marginal R^2/conditional R^2	0.254/0.862				
Model 6. Modifiable risk factors with treatment					
Fixed effects					
Intercept	15.53	11.06	20.00	**<0.001**	***
Time	−0.82	−1.03	−0.60	**<0.001**	***
Time^2	0.03	0.02	0.05	**<0.001**	***
Sociodemographic variables					
Age	−0.09	−0.14	−0.05	**<0.001**	***
Sex (ref: male)	−0.09	−0.67	0.49	0.760	
Living situation (ref: cohabitating)	0.11	−0.40	0.61	0.681	
Group allocation (ref: CAU)	−0.06	−0.68	0.56	0.850	
Potentially modifiable risk factors					
Education (ref: low)					
Moderate	−0.12	−0.76	0.52	0.711	
High	−1.24	−2.60	0.13	0.075	
Time×moderate	−0.19	−0.40	0.02	0.080	
Time×high	−0.47	−0.99	0.05	0.074	
Hearing impairment (ref: none)					
Uncompensated	0.43	−0.14	1.00	0.138	
Compensated	0.79	0.16	1.41	**0.014**	*
Depression (ref: none)	−1.25	−1.96	−0.54	**0.001**	**
Physical activity (ref: none)					
One activity	1.13	0.41	1.86	**0.002**	**
Two and more activities	1.33	0.61	2.05	**<0.001**	***
Diabetes (ref: none)					
Uncompensated	0.06	−0.56	0.68	0.847	
Compensated	0.40	−0.16	0.96	0.162	
Smoking (ref: nonsmoker)					
Used to	−0.20	−0.75	0.35	0.465	
Yes	1.05	−0.05	2.14	0.060	
Hypertension (ref: none)					
Uncompensated	0.29	−1.06	1.64	0.672	
Compensated	0.30	−0.38	0.98	0.391	
Obesity (ref: none)	−0.16	−0.91	0.60	0.687	
Alcohol consumption (ref: none)					
Less than daily	0.41	−0.09	0.91	0.106	
Daily	0.18	−0.77	1.14	0.704	

(Continues)

TABLE 3 (Continued)

Model 6. Modifiable risk factors with treatment					
Social support	−0.39	−0.82	0.04	0.073	
Visual impairment (ref: none)	−0.72	−1.21	−0.24	**0.003**	**
Random effects					
Intercept (person)	3.40				
Time	0.33				
Intercept (person)×time	0.11				
Intercept (GP)	0.35				
Residual	1.71				
ICC	0.81				
Marginal R^2/conditional R^2	0.258/0.861				

Abbreviations: CI, confidence interval, CAU, care as usual, GP, general practitioner.
$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$.

that visual impairment is a modifiable dementia risk factor: the treatment of eye diseases, for example, cataracts, is associated with lower dementia risk.[32–34] Optimal treatment of eye diseases in the population, therefore, may have the potential not only to reduce dementia risk in healthy adults and improve daily functioning but also to have a positive impact on the course of ADRD.

Finally, our findings suggest that the treatment of comorbidities can have a positive impact on the course of dementia: We found an association between treated diabetes and a slower cognitive decline over time. One possible explanation here lies in diabetes medication, and in particular metformin, for which there is increasing evidence of a neuroprotective effect for ADRD[35–37] and which is currently being specifically tested in a large dementia prevention study—in combination with lifestyle interventions.[38]

Although we were able to identify associations between some modifiable risk factors and symptom progression, we did not find associations for hypertension, alcohol consumption, obesity, smoking, lack of social support, and physical inactivity.

The lack of association with hypertension and obesity can be explained by the fact that individuals with dementia tend to lose weight due to the disease, so although obesity may increase the risk of developing dementia, it may not influence its progression.[39] The same applies to hypertension, as blood pressure tends to decrease again in individuals with dementia.[39] With alcohol consumption, a reporting bias is conceivable. People often respond to questions about their alcohol intake in a socially desirable manner or underreport their consumption.[40,41] The measurement method could also explain why we did not find an association between hearing impairment and cognitive decline: Measuring hearing impairment is methodologically challenging, and subjective reports often lack validity.[42] Many people are unaware of their hearing loss, and this is likely the case in our sample, as over half of our sample reported no impairment, despite higher prevalence rates in older adults in Germany (71.1% among 75- to 79-year-olds).[43] Therefore, some participants may have had unreported hearing impairment, whereas those aware of their impairment and using hearing aids may have been better cared for. With regard to smoking—which promotes neuropathological processes—it should be noted that there were very few active smokers in the sample, which likely reduced our ability to detect an association with cognitive or functional decline. We also found no association between social support and physical activity in cognitive and functional decline. However, using the same sample, it has already been shown that people with more social support had a higher life expectancy.[44] Therefore, social support seems to play a role in the health of people with ADRD, even if we did not find an association with cognitive or functional decline.

4.1 | Strengths and limitations

A major strength of this study is that it was conducted within the community, offering high external validity due to its proximity to the routine care setting. Another significant strength is the extensive data collected on the living and care situation of individuals with dementia over a long period, enabling the analysis of the role of many risk factors on symptom progression.

However, these strengths are accompanied by certain limitations. The DelpHi-MV trial was not a diagnostic trial but rather a trial conducted within the realm of care, which limits the information available on dementia etiology. In addition, the nature of the setting meant that not all health and lifestyle factors could be assessed in-depth using state-of-the-art methods. For example, hearing impairment and alcohol consumption were measured subjectively, which can lead to limitations in validity.[41,42] Moreover, the measurement of some lifestyle factors such as physical activity, smoking, and alcohol consumption using the STEP questionnaire was not comprehensive. For instance, only the number of physical activities in which a person engaged was recorded, without capturing their duration or frequency. Similarly, cognition was assessed using the MMSE, a dementia screening tool, rather than a more comprehensive measure of cognitive performance. Future studies must carefully address the challenge of collecting extensive data on the living and care situation from cognitively impaired individuals within a limited timeframe.

Finally, another limitation is the substantial attrition rate over the 8-year period, primarily due to the advanced age and chronic illness of the participants. Nevertheless, to ensure robust modeling, only individuals with at least two measurements of cognition and daily functioning were included in the analysis. Furthermore, the statistical methods employed have the advantage of effectively managing missing data in the dependent variables.[45]

5 | CONCLUSION

In our study, we found evidence of the role of several potentially modifiable risk factors for symptom progression in dementia over up to 8 years. We observed an effect of cognitive reserve through education, which reversed over the course of the study. In addition, depressive symptoms were associated with less favorable symptom progression. Our study suggests that treating comorbidities (such as diabetes and visual impairment) could have a positive impact on the course of dementia symptoms. These modifiable risk factors are promising targets for tertiary prevention and should be further investigated in intervention trials.

ACKNOWLEDGMENTS

We acknowledge Ines Abraham, RN; Ulrike Kempe, RN; Sabine Schmidt, RN; Vaska Böhmann, RN; Kathleen Dittmer, RN; and Saskia Moll, RN (Greifswald Medical School, University of Greifswald, Greifswald, Germany) for data collection and intervention delivery. We also acknowledge Daniel Fredrich, Dipl-Inf (Greifswald Medical School, University of Greifswald, Greifswald, Germany), and Henriette Rau, MSc (German Center for Neurodegenerative Diseases [DZNE], Rostock/Greifswald, Germany) for information technology development and support in conducting the trial. In addition, we acknowledge Kerstin Albuerne, MedDok, and Andrea Pooch, BSc (DZNE, Rostock/Greifswald, Germany), for data collection, data quality assurance, and data provision; and Viktoria Kim-Boese, MSc and Kerstin Wernecke, PhD (DZNE Rostock/Greifswald, Germany) for writing and editing assistance as well as administrative assistance in conducting the trial. We express our gratitude to all patients, caregivers, and general practitioners who took part in this study. The present study was funded by the Alzheimer Forschung Initiative e.V. (AFI).

Open access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST STATEMENT

R.T. is a member of the boards of directors of the German Alzheimer Society (Deutsche Alzheimer Gesellschaft e. V.) and Alzheimer Europe. S.T. served on the advisory board for Roche, Eisai, and Biogen and is a member of the independent data monitoring board of the study ENVISION (Biogen). B.M. received consulting fees from Biogen. The remaining authors have no conflicts to disclose.

CONSENT STATEMENT

The study received ethical approval from the ethics committee of the Chamber of Physicians of Mecklenburg-Western Pomerania—registry number: BB 20/11. Prior to participation, all human subjects provided written informed consent.

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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: Blotenberg I, Wittström F, Michalowsky B, et al. Modifiable risk factors and symptom progression in dementia over up to 8 years—Results of the DelpHi-MV trial. *Alzheimer's Dement*. 2025;17:e70050. https://doi.org/10.1002/dad2.70050