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Factors associated with dropout in the longitudinal Vogel study of cognitive decline

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Abstract

Dementia, including Alzheimer's disease, is a growing problem worldwide. Prevention or early detection of the disease or a prodromal cognitive decline is necessary. By means of our long-term follow-up 'Vogel study', we aim to predict the pathological cognitive decline of a German cohort (mean age was 73.9 ± 1.55 years at first visit) with three measurement time points within 6 years per participant. Especially in samples of the elderly and subjects with chronic or co-morbid diseases, dropouts are one of the biggest problems of long-term studies. In contrast to the large number of research articles conducted on the course of dementia, little research has been done on the completion of treatment. To ensure unbiased and reliable predictors of cognitive decline from study completers, our objective was to determine predictors of dropout. We conducted multivariate analyses of covariance and multinomial logistic regression analyses to compare and predict the subject's dropout behaviour at the second visit 3 years after baseline (full participation, partial participation and no participation/dropout) with neuropsychiatric, cognitive, blood and lifestyle variables. Lower performance in declarative memory, attention and visual–spatial processing predicted dropout rather than full participation. Lower performance in visual–spatial processing predicted partial participation as opposed to full participation. Furthermore, lower performance in mini-mental status examination predicted whether subjects dropped out or participated partially instead of full participation. Baseline cognitive parameters are associated with dropouts at follow-up with a loss of impaired participants. We expect a bias into a healthier sample over time.

Abbreviations: AD, Alzheimer's disease; ADI, Alzheimer's Disease International; ANOVA, analysis of variance; ASI-3, Anxiety Sensitivity Index-3; B-ADL, Bayer-Activities of Daily Living Scale; BDI-II, Beck Depression Inventory-II; BDNF, brain-derived neurotrophic factor; BMI, body mass index; CFT, Rey Complex Figure Test; CI, confidence interval; DemTect, dementia detection test; EDTA, ethylenediaminetetraacetate; EFA, exploratory factor analysis; GDS, geriatric depression screening scale; M, mean; MANCOVA, multivariate analysis of (co-)variance; MCI, mild cognitive impairment; MD, mean difference; MMSE, mini-mental status examination; MRI, magnetic resonance imaging; OR, odds ratio; RT, reaction time; RWT, Regensburger Verbal Fluency Test ('Regensburger Wortflüssigkeitstest'); SD, standard deviation; SE, standard error; SEM, structural equation modelling; TAP, battery of Tests for Attentional Performance; VLMT, Verbal Learning and Memory Test; WHO, World Health Organization; WMS-R, Wechsler Memory Scale-Revised.

KEYWORDS
Alzheimer's disease, cognitive decline, dropout, elderly, mild cognitive impairment (MCI), prediction

1 | INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia (60%–70% of cases) and one of the most frequent neurodegenerative disorders (World Health Organization [WHO], 2019). An irreversible, progressive course is characteristic (Yang et al., 2018). Worldwide, around 50 million people have dementia (WHO, 2019). Experts estimate the number to be as high as 82 million by 2030 and an alarming 152 million by 2050, mainly due to the growing elderly population (WHO, 2019). The total cost of dementia in 2019 was estimated at around US$1 trillion and is expected to rise to US$2 trillion by 2030 (Alzheimer's Disease International, 2019; Handels et al., 2018; Reed et al., 2019). Currently, no curative drug therapy is available (Meyer et al., 2020).

Therefore, the prevention of the disease is mandatory. The exploration of risk factors and predictors of dementia or the characteristically prodromal cognitive decline could make this possible (Hickman et al., 2016; Jessen, 2019; Qian et al., 2017). Extensive reviews postulated the predictive validity for various risk factors, besides age (WHO, 2019). For example, early-life factors like the education level or family-related factors (Wang et al., 2019) and modifiable lifestyle factors such as alcohol consumption, physical activity or the body mass index (BMI) have the potential to be of predictive value (Li et al., 2020; Peters et al., 2019; Xu et al., 2015). Also, chronic or pre-existing diseases such as heart, vascular or psychiatric diseases (Larsson & Markus, 2018), biophysiological variables like the brain-derived neurotrophic factor (BDNF) and blood parameters, and genetics such as the phenotypes of Apolipoprotein-ϵ4ϵ4/ϵ3ϵ4 do play an important role (Sharma et al., 2020; Sun et al., 2015). Moreover, the cognitive performance level should be examined (Li et al., 2016; Song et al., 2018).

By means of our long-term follow-up 'Vogel study', we aim to predict a cognitive decline of a German cohort (>600 people, >70 years) over a total of 10 years, with 6 years of single participant observation and three visits. High dropout rates mean a loss of information and, therefore, biased predictions of cognitive decline and decreased statistical power. Hence, study completion is essential to find reliable predictors. A lack of understanding of the dropout behaviour in our study even could increase the rate. Especially within samples of the elderly and subjects with chronic or co-morbid diseases, dropouts are one of the biggest problems of long-term studies (Hill et al., 2016; Waring et al., 2005). Reasons for dropout vary and may occur due to illness, death, institutionalization, refusal of participation, failed contact or lack of interest (Burke et al., 2019; Coley et al., 2008). In contrast to the research conducted on the course of dementia, still only a few research has been conducted on study completion or predictors for dropout in longitudinal AD studies (e.g. Agogo et al., 2018; Coley et al., 2011; Das et al., 2018; Mehdipour Ghazi et al., 2019; Tan et al., 2018). Some revealed predictive factors influencing dropouts in longitudinal investigations of dementia/AD samples. For instance, researchers found out that a progressing cognitive impairment, more neuropsychiatric symptoms or specific bio-physiological features are predictors for dropout using data of 35 US-American AD centres (Burke et al., 2019). Another study stated the relevance of weaker cognitive functioning using the mini-mental status examination (MMSE), symptoms of depression, higher age and disability at baseline in a dementia prevention study (Beishuizen et al., 2017). Others found out that impaired cognitive functioning using the MMSE and dementia assessment scales and depressive symptoms could predict dropout in patients with mild cognitive impairment (MCI) and AD (Lo & Jagust, 2012). Moreover, the degree of need for care, the use of cholinesterase inhibitors or other drugs predicted dropout in another multicentre AD cohort (Coley et al., 2008). A further study investigated future dementia risk, evidenced by prior brain magnetic resonance imaging (MRI) scans, as a predictive factor associated with dropout (Glymour et al., 2012).

Based on recent findings considering the dropout behaviour of the elderly, this study aimed to investigate our sample characteristics, examine the dropout behaviour of the participants and determine predictors of dropout. On these terms, we tried to find reliable predictors of cognitive decline from study completers.

2 | METHODS

2.1 | Sample characterization

$N = 604$ subjects (age: 70–77 years) participated in the baseline investigation of the 'Vogel study', which is a long-term, observational and prospective study including

two follow-ups. With a total study duration of 10 years and 6 years of individual monitoring, the study aims to detect MCI or AD early and find predictors and risk factors of pathological cognitive decline. It was approved by the local ethics committee and was in accordance with the Helsinki Declaration (vote no. 23/11; World Medical Association, 2013). For participant recruitment, 5124 inhabitants of the city of Würzburg, born between April 1936 and March 1941, were contacted by letter, and invited to our information session after receiving the contact information of 7875 age-appropriate inhabitant records from the registry department. Then, following the random and stepwise postal invitations of 200 potential participants each to information sessions, interested individuals were registered for the first screening.

The following exclusion criteria were applied: (1) a severe neurologic, psychiatric or internal disease within the past year; (2) a severe, uncorrected and impaired vision or hearing; and (3) the use of psychoactive medication at the baseline investigation. In addition, each subject confirmed the participation in the study in a written declaration of consent after receiving complete information. Hence, sample recruitment was done randomly to get a representative sample. However, it can be assumed that, for example, certain personality traits, the level of education, cognitive deficits or socio-economic status influence the willingness to participate in the study. The representativeness of the sample might therefore be restricted.

To control for confounding variables in statistical analyses and to ensure comparability with previous findings (Haberstumpf et al., n.d.; Haberstumpf et al., 2020; Katzorke et al., 2017, 2018; Polak et al., 2017; Zeller et al., 2019), we excluded $n = 65$ participants due to a history of a central nervous system disease that may affect their cognitive performance (multiple sclerosis, epilepsy, pain syndrome, restless legs syndrome, stroke, head injury, traumatic brain injury, cerebral bleeding, transient ischaemic attack and basal skull fracture). Furthermore, we excluded $n = 12$ participants who died until the first follow-up because of the lack of information about the cause of death to avoid confounding variables. Until the first follow-up, we had a dropout group with a total of $n = 78$ participants. Of those, $n = 56$ participants did not participate anymore or dropped out due to a refusal to participate in further investigations, $n = 22$ participants because they could no longer be reached (e.g. per phone, unknown removals). Those who participated fully ($n = 333$) and partially ($n = 116$; e.g. reduced neuropsychiatric diagnostics or domiciliary visits) remained, resulting in a total of $n = 527$ participants until the completion of the first follow-up (see Figure 1). We examined demographic characteristics with frequency analyses, chi-square tests (sex and type of housing) and one-way analyses of variance (ANOVAs; age, education level). Of $n = 271$ males and $n = 256$ females at first follow-up, more females were in the dropout and partial participation group at first follow-up than males, whereas more males participated fully ($\chi^2 = 8.24$, $p = 0.016$). Groups also differed in age ($F_{(2,\ 534)} = 5.61$, $p = 0.004$, $\eta^2 = 0.02$): Subjects with full participation (Mean [M] = 73.72, standard deviation [SD] = 1.55, $n = 333$) were younger than dropouts ($M = 74.23$, $SD = 1.44$, $N = 78$; $p = 0.025$) and subjects with partial participation ($M = 74.14$, $SD = 1.55$,

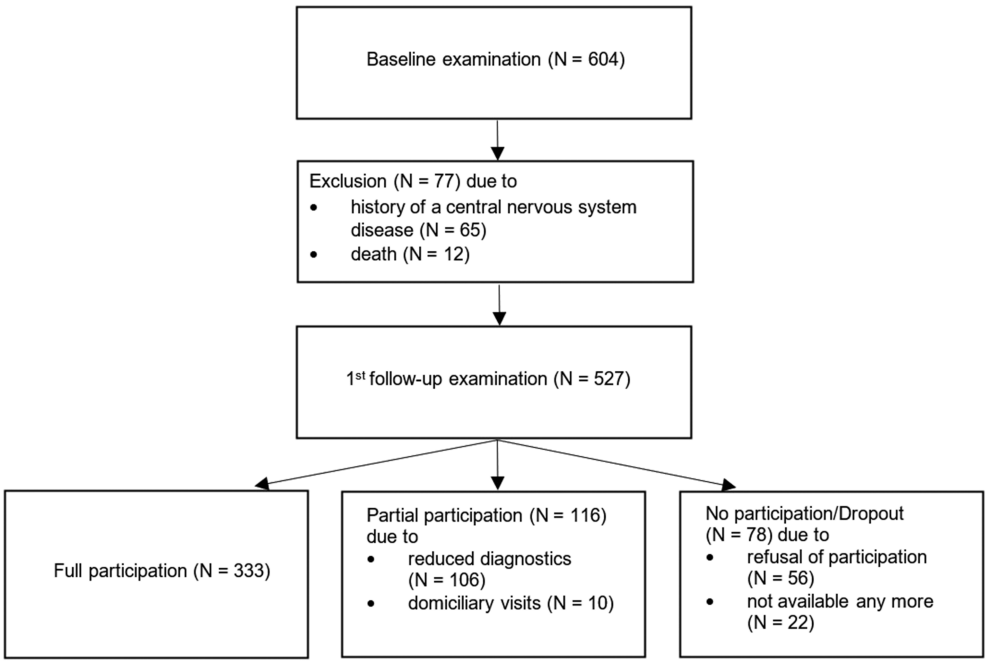

FIGURE 1 Course of exclusion for data analysis

$N = 126$; $p = 0.030$). The dropout groups only tended to differ in education level ($F_{(2,\ 520)} = 2.52$, $p = 0.081$, $\eta^2 = 0.01$; see Table 1). Moreover, groups did not differ in type of housing (alone/with relatives/other: $\chi^2 = 7.62$, $p = 0.106$; room/apartment/house: $\chi^2 = 4.03$, $p = 0.673$). Based on model assumptions and our previous work (Polak et al., 2017; see also the Section 5), we applied sex, age (years) and education level (grades) as covariates for further analyses of the predictive value of neuropsychiatric tests and blood and lifestyle variables for predicting study dropout at first follow-up.

2.2 | Neuropsychiatric diagnostics

We conducted different neuropsychiatric tests for the diagnostic characterization of our sample. Firstly, we measured cognitive performance with a specific test battery including the Verbal Learning and Memory Test (VLMT; Helmstaedter et al., 2001), the Wechsler Memory Scale-Revised (WMS-R; Härting et al., 2000), subtests tonic and phasic alertness of the battery of Tests for Attentional Performance (TAP; Fimm & Zimmermann, 2001), the Regensburger Verbal Fluency Test (RWT; Aschenbrenner et al., 2000) and the Rey Complex Figure Test (CFT; Meyers & Meyers, 1996).

We further investigated a participant's affectivity by using the Beck Depression Inventory-II (BDI-II; Beck et al., 1996), the Geriatric Depression Screening Scale (GDS; Yesavage et al., 1982) and the Anxiety Sensitivity Index-3 (ASI-3; Reiss et al., 1986).

The state of neurodegeneration was assessed by using both the dementia detection test (DemTect; Kalbe et al., 2004) as well as the MMSE (Folstein et al., 1975) as dementia screenings.

A participant's autonomy in daily routine was objectified using the Bayer-Activities of Daily Living scale (B-ADL; Hindmarch et al., 1998). The B-ADL was assessed as an interview procedure, and the participants' functional level was therefore self-rated by them at the baseline. This was feasible due to the initial, mostly non-demented state of the participants.

2.3 | Blood and lifestyle variables

We took blood as an empty-stomach blood test for routine and exploratory laboratory parameters (serum, ethylenediaminetetraacetate [EDTA] plasma) on baseline investigation (see Table 2) and obtained lifestyle variables based on anamnestic questions: We classified the education level by the participant's statements to their graduate level. Substance consumption variables describe the

TABLE 2 Blood analysis

Collected blood parameters
Glucose (mg/dl)
Total cholesterol (mg/dl)
LDL-cholesterol (mg/dl)
HDL-cholesterol (mg/dl)
Triglycerides (mg/dl)
Leucocytes (n*1000/µl)
C-reactive protein (mg/dl)
Blood sedimentation rate: 1 h (mm)
Blood sedimentation rate: 2 h (mm)
Thyroid-stimulation hormone (ml/U/L)
Vitamin B12 (pg/ml)
Folacin (ng/ml)
Homocysteine (µmol/l)
HbA1c (%)
BDNF (ng/ml)

Abbreviation: BDNF, blood derived neurotrophic factor.

TABLE 1 Sample characterization

	No. of participation/dropout	Partial participation	Full participation	Total sample
N (male/female)	78 (35/43)	116 (49/67)	333 (187/146)	527 (271/256)
Age in years (range)	74.2 ± 1.44 (71–77)	74.2 ± 1.58 (70–77)	73.7 ± 1.55 (70–77)	73.9 ± 1.55 (70–77)
Education level (N, %)	77, 14.7	115, 22.0	331, 63.3	523, 100.0
Main school	35, 44.9	59, 50.9	140, 42.0	234, 44.4
Middle school	19, 24.4	31, 26.7	87, 26.1	137, 26.0
High school	11, 14.1	11, 9.5	35, 10.5	57, 10.8
University	12, 15.4	14, 12.1	69, 20.7	95, 18.2

Abbreviations: CFT, Rey Complex Figure Test (Meyers & Meyers, 1996); RT, reaction time; RWT, Regensburger Verbal Fluency Test (Aschenbrenner et al., 2000); TAP, battery of Tests for Attentional Performance (Fimm & Zimmermann, 2001); VLMT, Verbal Learning and Memory Test (Helmstaedter et al., 2001); WMS-R, Wechsler Memory Scale-Revised (Härting et al., 2000).

subject's dichotomous consumer behaviour at baseline investigation (cigarettes, alcohol and caffeine). Finally, we asked for familial predispositions developing dementia/AD (e.g. known AD diagnosis in previous family generations) and calculated the BMI.

3 | DATA ANALYSIS

3.1 | Cognitive performance

To quantify a participant's cognitive performance, we used the following 11 neuropsychiatric test variables of our 527 participants without a history of a central nervous system disease at baseline investigation: VLMT immediate recall (sum score words), VLMT delayed recall (sum score reproduced words), VLMT recognition (sum score recognition word list), WMS-R digit span (sum score), WMS-R block span (sum score), TAP tonic alertness (median of reaction time [RT]), TAP phasic alertness (parameter for phasic alertness), RWT verbal fluency (sum score) and RWT category fluency (sum score), CFT memory (sum score) and CFT visuoconstruction (drawing score). Based on the theoretical background (National Institute of Mental Health, 2011) and preliminary structural equation modelling (SEM) in a naturalistically smaller, more restricted sample described in Haberstumpf et al. (n.d.), we identified four latent factors within our neuropsychiatric test variables that showed measurement invariance from baseline investigation to first follow-up. Hence, in our current analysis, we calculated values for each participant at baseline extracted by an exploratory factor analysis (EFA), following Eigenvalue and parallel analysis (see Table 3). After varimax rotation, factor loadings ≥0.4 were extracted in the model. All statistical requirements were met (Kaiser–Meyer–Olkin criterion: 0.758, Bartlett's test of sphericity: $\chi^2(55) = 1486.78$, $p < 0.001$). Actual EFA revealed the same four factors for the baseline sample as described in Haberstumpf et al. (n.d.), which simultaneously confirms the previously latent factors and their stability over time: declarative memory (consisting of all three VLMT scores), working memory (both RWT scores and WMS-R digit span), attention (TAP tonic and phasic alertness) and visual–spatial processing (both CFT scores and WMS-R block span).

3.2 | Statistical analysis

We analysed demographical, neuropsychiatric, biological and clinical data using baseline data and performed all computations in IBM SPSS Statistics for Windows (version 25). As possible, we presented data as $M \pm SD$. The two-tailed α significance level was set at $p < 0.05$.

3.3 | Multivariate analyses of covariance

We conducted multivariate analyses of covariance (MANCOVA) to compare the independent subject's dropout behaviour (full participation, partial participation and no participation/dropout) at first follow-up with diverse dependent variables to detect between-group differences, including the covariates sex, age, and education

TABLE 3 Neuropsychiatric factors defined by exploratory factor analysis (EFA)

		Factor loadings after varimax rotation			
Extracted factor	**Test variables**	**1**	**2**	**3**	**4**
Declarative memory	VLMT immediate recall	0.895	-	-	-
	VLMT delayed recall	0.838	-	-	-
	VLMT recognition	0.810	-	-	-
Attention	TAP tonic alertness	-	0.748	-	-
	TAP phasic alertness	-	0.688	-	-
Working memory	WMS-R digit span	-	-	0.624	-
	RWT verbal fluency	-	-	0.779	-
	RWT category fluency	-	-	0.808	-
Visual–spatial processing	WMS-R block span	-	-	-	0.510
	CFT memory	-	-	-	0.793
	CFT visuoconstruction	-	-	-	0.727

Abbreviations: CFT, Rey Complex Figure Test (Meyers & Meyers, 1996); RT, reaction time; RWT, Regensburger Verbal Fluency Test (Aschenbrenner et al., 2000); TAP, battery of Tests for Attentional Performance (Fimm & Zimmermann, 2001); VLMT, Verbal Learning and Memory Test (Helmstaedter et al., 2001); WMS-R = Wechsler Memory Scale-Revised (Härting et al., 2000).

level. We specified the effects of our covariates by calculating correlations with dependent variables. Moreover, we used individual one-way ANOVAs and Bonferroni corrected post-hoc tests to examine differences for each group and avoid α-error-cumulation. Finally, we followed up significant MANCOVAs with multinomial logistic regression analyses.

3.4 | Multinomial logistic regression analysis

We performed multinomial logistic regression analyses to examine the predictors of study dropout at the first follow-up investigation. We used our multinomial variable dropout behaviour with three outcome categories (full participation, partial participation and no participation/dropout) at first follow-up as the dependent variable. Predictors were treated as continuous variables. Exceptions were our covariate sex and our categorical variables familial predisposition for dementia/AD, cigarette consumption, alcohol consumption and caffeine consumption. We entered all variables as main effects for univariate analyses. The relationship between our predictors and the variable dropout behaviour was assessed by estimating odds ratios with 95% confidence intervals (ORs, 95% CI), indicating an increased probability of a subject's participation at the first follow-up investigation when OR > 1. Otherwise (OR < 1), our predictor variable will indicate an increased probability of a study dropout at the first follow-up investigation per every unit added.

4 | RESULTS

4.1 | Multivariate between-group comparisons of baseline sample characteristics

4.1.1 | Cognitive performance

Using the multivariate Pillai's trace, we found significant effects between the four factors describing the participant's cognitive performance at baseline investigation and their dropout behaviour at first follow-up ($V = 0.06$, $F_{(8,\ 1008)} = 3.58$, $p < 0.001$, $\eta^2 = 0.028$; see Table S1). The univariate tests showed significant effects for three of the four factors: declarative memory ($F_{(2,\ 506)} = 3.73$, $p = 0.025$, $\eta^2 = 0.015$), attention ($F_{(2,\ 506)} = 3.28$, $p = 0.038$, $\eta^2 = 0.013$) and visual–spatial processing ($F_{(2,\ 506)} = 5.33$, $p = 0.005$ $\eta^2 = 0.021$).

Bonferroni corrected post-hoc tests showed significant lower performances of declarative memory for participants who dropped out compared with those who participated fully at first follow-up (mean difference [MD] $= -0.33$, $p = 0.020$). It also revealed significantly lower attention performances for participants who dropped out compared with full participants (MD $= -0.30$, $p = 0.046$). Moreover, Bonferroni correction revealed significantly lower attention performances for partial participants compared with full participants at first follow-up (MD $= -0.39$, $p = 0.032$). Significantly lower performances of visual–spatial processing for participants who dropped out compared with full (MD $= 0.30$, $p = 0.046$) and partial participants (MD $= 0.29$, $p = 0.023$) could also be found (see also Figure 2).

Highly significant group differences appeared for participants with higher education level performing better in declarative memory ($F_{(1,\ 506)} = 16.86$, $p < 0.001$, $\eta^2 = 0.032$), working memory ($F_{(1,\ 506)} = 64.85$, $p < 0.001$, $\eta^2 = 0.114$) and visual–spatial processing

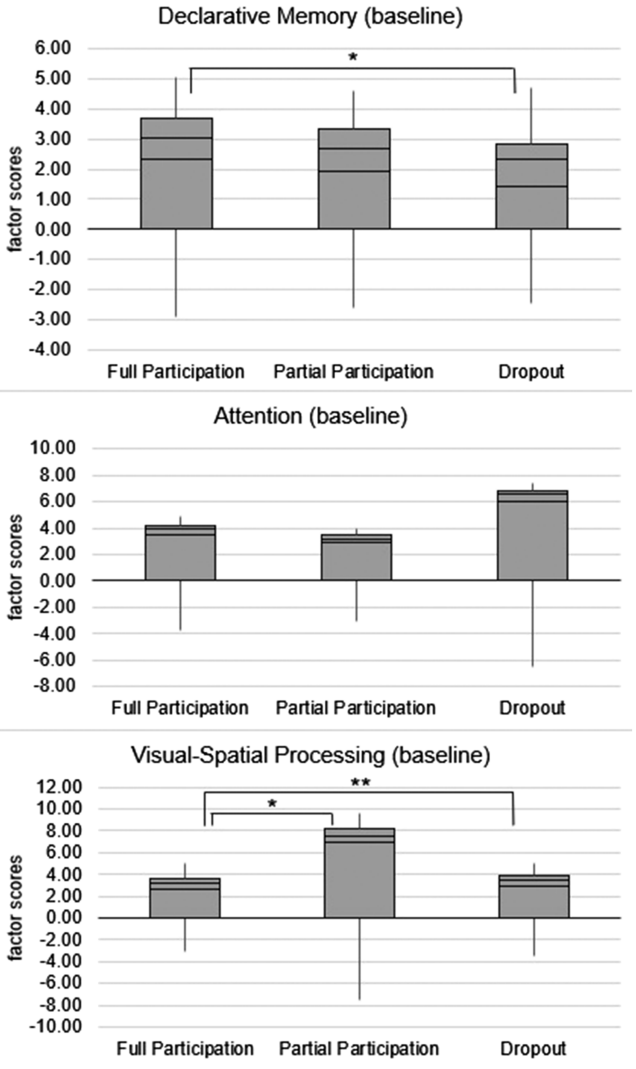

FIGURE 2 Significant factor scores of cognitive performances for subject's dropout behaviour

($F_{(1,\ 506)} = 13.79$, $p < 0.001$, $\eta^2 = 0.027$) as well as for female gender performing better in declarative memory ($F_{(1,\ 506)} = 67.63$, $p < 0.001$, $\eta^2 = 0.118$) and male gender scoring higher in visual–spatial processing ($F_{(1,\ 506)} = 18.86$, $p < 0.001$, $\eta^2 = 0.036$).

4.1.2 | Affectivity

Pillai's trace showed a significant effect for the subject's dropout behaviour on the psychiatric test scores measuring affectivity (BDI-II, GDS, ASI-3; $V = 0.03$, $F_{(6,\ 1012)} = 2.18$, $p = 0.043$, $\eta^2 = 0.01$; see Table S2). However, univariate tests for all three affectivity test scores revealed no significant effects.

4.1.3 | Dementia screenings

Pillai's trace revealed significant effects between dropout behaviour at first follow-up investigation and the two cognitive test scores describing participant's state of neurodegeneration at baseline investigation (MMSE, DemTect; $V = 0.04$, $F_{(4,\ 1034)} = 5.36$, $p < 0.001$, $\eta^2 = 0.02$; see Table S3). Both univariate analyses were significant (MMSE: $F_{(2,\ 517)} = 9.97$, $p < 0.001$, $\eta^2 = 0.04$; DemTect: $F_{(2,\ 517)} = 3.80$, $p = 0.023$, $\eta^2 = 0.01$).

Bonferroni corrected post-hoc tests showed highly significant lower performance in the MMSE performance for participants that dropped out compared with participants that participated fully at first follow-up (MD = −0.64, $p < 0.001$) and significantly lower performance for subjects with partial instead of full participation at first follow-up (MD = 0.33, $p = 0.038$). Moreover, Bonferroni correction revealed significantly lower DemTect scores for subjects who dropped out compared with subjects with full participation at first follow-up (MD = −0.73, $p = 0.021$; see also Figure 3).

Again, highly significant group differences could be revealed for higher educated participants reaching higher test scores in the MMSE ($F_{(1,\ 517)} = 18.46$, $p < 0.001$, $\eta^2 = 0.034$) and the DemTect ($F_{(1,\ 517)} = 16.26$, $p < 0.001$, $\eta^2 = 0.030$) as well as for better performances of the female gender in the DemTect ($F_{(1,\ 517)} = 16.67$, $p < 0.001$, $\eta^2 = 0.031$).

4.1.4 | Autonomy in daily routine

Regarding participant's dropout behaviour at follow-up investigation, no significant between-subjects effects could be found for B-ADL ($F_{(2,\ 517)} = 0.059$, $p = 0.943$, $\eta^2 = 0.00$; see Table S4).

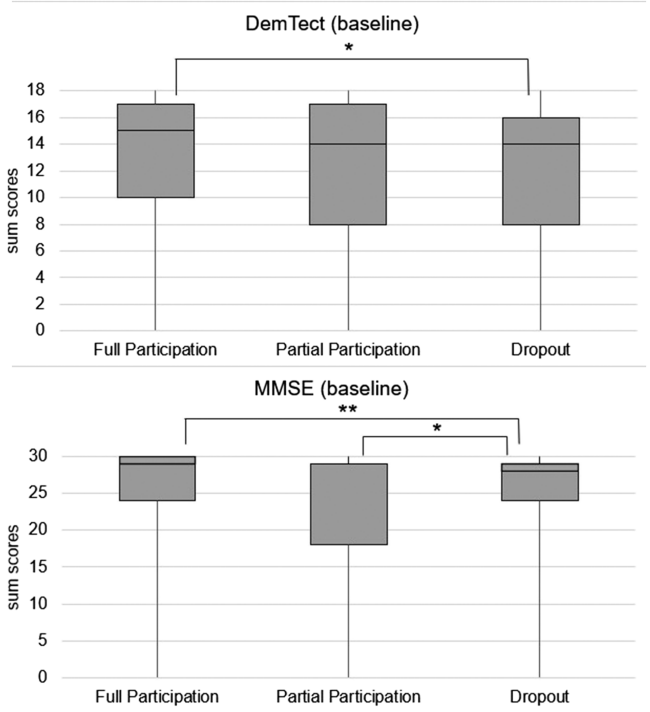

FIGURE 3 Significant sum scores of dementia screening diagnostics for subject's dropout behaviour. DemTect, dementia detection test (Kalbe et al., 2004); MMSE, mini-mental state examination (Folstein et al., 1975)

4.1.5 | Blood and lifestyle variables

Pillai's trace did not find any significant differences between blood and lifestyle factors and the participant's dropout behaviour at first follow-up investigation ($V = 0.06$, $F_{(32,\ 984)} = 9.7$, $p = 0.52$, $\eta^2 = 0.03$; see Table S5).

4.2 | Prediction of dropout behaviour at first follow-up investigation

4.2.1 | Cognitive performance

As can be seen in Table S6, individual multinomial logistic regression analysis ($R^2 = 0.10$ (Cox–Snell); model $\chi^2(14) = 52.02$, $p < 0.001$) revealed that study dropout could be predicted by three of the four factors. Lower performance in declarative memory at baseline significantly predicted dropout at first follow-up rather than full participation ($b = -0.38$, standard error [SE] = 0.14, Wald's $\chi^2(1) = 7.18$, $p = 0.007$, OR = 0.69). Also, analyses showed that lower performance in attention at baseline significantly predicted dropout at first follow-up instead of full participation ($b = -0.33$, $SE = 0.16$, Wald's $\chi^2(1) = 4.13$, $p = 0.042$, OR = 0.72). Additionally, deficits in

visual–spatial processing significantly predicted dropout at baseline compared with full participation at first follow-up ($b = -0.37$, $SE = 0.14$, Wald's $\chi^2(1) = 7.35$, $p = 0.007$, OR = 0.69).

Referring to participants who participated partially at first follow-up, performance deficits could draw significant predictions for the factor visual–spatial processing ($b = -0.32$, $SE = 0.12$, Wald's $\chi^2(1) = 7.29$, $p = 0.007$, OR = 0.73).

Furthermore, our covariates male sex and higher age significantly predicted study dropout (sex: $b = -0.60$, $SE = 0.30$, Wald's $\chi^2(1) = 3.96$, $p = 0.047$, OR = 0.55; age: $b = 0.16$, $SE = 0.13$, Wald's $\chi^2(1) = 1.55$, $p = 0.214$, OR = 1.17), but male sex was the only covariate predicting partial participation as opposed to full participation at first follow-up (sex: $b = -0.54$, $SE = 0.25$, Wald's $\chi^2(1) = 4.68$, $p = 0.030$, OR = 0.58). Unlike significant group differences in various test procedures (Table S1), the education level could not significantly predict the dropout behaviour.

4.2.2 | Dementia screenings

As can be seen in Table S7, subject's lower performance in MMSE predicted (highly) significant whether subjects dropped out ($b = -0.37$, $SE = 0.11$, Wald's $\chi^2(1) = 11.19$, $p = 0.001$) or participated partially at first follow-up ($b = -0.26$, $SE = 0.10$, Wald's $\chi^2(1) = 6.44$, $p = 0.011$) as opposed to full participation ($R^2 = 0.08$ (Cox–Snell); model $\chi^2(12) = 45.49$, $p < 0.001$). Both covariates male sex and higher age (highly) significantly predicted dropout (sex: $b = -0.65$, $SE = 0.27$, Wald's $\chi^2(1) = 5.87$, $p = 0.015$; age: $b = 0.25$, $SE = 0.09$, Wald's $\chi^2(1) = 8.10$, $p = 0.004$) or partial participation (sex: $b = -0.66$, $SE = 0.23$, Wald's $\chi^2(1) = 8.42$, $p = 0.004$; age: $b = 0.20$, $SE = 0.07$, Wald's $\chi^2(1) = 7.12$, $p = 0.008$) rather than full participation at first follow-up. Again, no significant effects could be found for the education level as a predictor of dropout behaviour compared with significant group differences in the dementia screenings (see Table S3).

5 | DISCUSSION

In this study, we investigated the predictive effects of several demographical, biological and clinical variables assessed at the baseline investigation on dropout behaviour at first follow-up in the elderly participants of the Vogel study. Multinomial logistic regression analyses revealed that deficits in cognitive performance predict study dropout. More precisely, lower performance in declarative memory, attention and visual–spatial processing at baseline investigation predicted dropout at first follow-up rather than full participation. Also, lower performance in visual–spatial processing at baseline investigation significantly predicted partial participation instead of full participation at first follow-up. However, as we saw in MANCOVA and logistic regression analysis, working memory could not predict dropout behaviour. Concerning the covariates analysed, older age at baseline and male sex predicted study dropout. In addition, the male sex decreased the likelihood of partial participation.

These results seem plausible, as lower performance in declarative memory, due to memory loss, could be one of the first signs of MCI or AD (Bryzgalov et al., 2018; Jahn, 2013; Nestor et al., 2006; Riedel & Blokland, 2015; Vakalopoulos, 2017). If we assume that participants with lower performance in declarative memory are beginning to suffer from MCI or dementia, this could explain dropout, and we must expect a smaller number of participants with diagnosed MCI or AD at the follow-ups. In reverse, the long-term prediction of cognitive decline will get complicated. Researchers also suggest that declarative memory remains functional for a long time in neurodevelopmental disorders because of suspected compensatory mechanisms (Ullman & Pullman, 2015). Hence, lower performance in declarative memory could indicate the progression from prodromal symptoms to disease, which also increases the probability of dropout. Contrary, it is possible that the participant's routine with research methods, for example, diagnostics, plays a role in further study participation. We assume that the probability of refusal thereby is smaller. Familiarity with cognitive tests, and therefore a higher retrieval frequency, affects memory performance more than memory age (Muller et al., 2014). Interestingly, research also discusses the relationship between memory and attention in AD in the sense of impaired attention performance accompanying memory deficits from early prodromal AD stages (Finke et al., 2013). Links between attention and visual–spatial processing performance are also conceivable: Poorer outcomes are possible due to visual search. The authors described both visuospatial attention and visual search deficits in early AD (Ramzaoui et al., 2018). Following memory research, visual–spatial impairment is an essential contributor to cognitive deficits and leads to the pathological development of dementia (Fernandez et al., 2018; Maharani et al., 2018, 2019). To strengthen findings concerning visual–spatial processing performance, other sensory impairments like auditory deficits should be assessed to predict dropout or cognitive decline (Zhao et al., 2015). We think that cognitive performance itself has a great potential to predict study dropout. Thus, it might be helpful to replicate our findings to specify the effect of our defined factors on dropout, expecting further

effects for working memory as a predictor at a more progressive stage.

Our MANCOVAs showed no significant effects between affectivity test scores and dropout behaviour, which is why we renounced regression analysis. Affective disorders are characterized by variability and instability over time (de la Vega et al., 2018). Therefore, it is difficult to predict the participant's health 3 years later. We had no information about the occurrence, remission rate or chronification status of a participant's affective impairment. Furthermore, the ASI-3 is the only test we used to assess anxiety. This test measures anxiety as a trait. Traits are more stable over time than states, which is why we assume that a trait score is more suitable for prediction. It might be important to do more research with various appropriate diagnostics on this topic, regarding their predictive potential (Beishuizen et al., 2017; Burke et al., 2019; Lo & Jagust, 2012).

Concerning the state of neurodegeneration, our statistical analyses showed that only the MMSE test score had a predictive effect on dropout behaviour. Lower performance in MMSE predicted study dropout or partial participation rather than full participation at first follow-up. Confirmed by research that the MMSE is one of the most frequently used screening questionnaires for assessing cognitive impairment, we think this finding is highly reliable (Arevalo-Rodriguez et al., 2015). Possibly, these participants needed reduced neuropsychiatric diagnostics at first follow-up, domiciliary visits, moved to nursing homes or were not accessible anymore. As already mentioned, other studies support the predictive value of the MMSE as a predictor for study dropout (Beishuizen et al., 2017; Lo & Jagust, 2012). Earlier MANCOVAs showed significant differences between study dropout and full participation at first follow-up concerning the subject's DemTect performance. However, the DemTect could not predict dropout. It is known that both DemTect and MMSE measure a similar construct but different cognitive domains (Beyermann et al., 2013).

Hence, we suggest that a subject's performance in these dementia screenings correlates with dropout (e.g. declarative memory $p < 0.029$, MMSE $p < 0.001$). Therefore, longitudinal research is particularly difficult because the sample that still participates fully at follow-up probably reflects a biased, healthier sample than expected in the future.

Regarding autonomy in daily routine, we found no significant effect for B-ADL as a predictor of dropout, although corresponding impairment may be a preclinical indicator of later MCI/AD progression and, thus, may also predict dropout (Cloutier et al., 2021).

Lastly, our MANCOVAs showed no significant effects between blood and lifestyle variables and dropout behaviour. However, research focusing on blood and lifestyle variables seems very promising for general future dementia research and could be a chance to predict dropout (Masley et al., 2017; Preische et al., 2019).

Overall, also the findings concerning the covariates predicting dropout behaviour delivered valuable information. First, older age predicted dropout or partial participation. In the current analysis, we examined a sample of older participants (aged ≥70 years), some of whom were in the risk group for developing MCI or AD. It is known that age is one of the strongest predictors of neurodegeneration and cognitive decline, respectively (Beishuizen et al., 2017; Podcasy & Epperson, 2016; Schneider et al., 2015; Sengoku, 2020). Thus, if cognitively more impaired participants dropped out of the study or were too impaired for full participation, this would explain old age as a predictor. Second, sex is an often discussed and significant predictor of cognitive changes (Kim et al., 2015). In terms of AD, the female sex mainly predicts disease progression instead of the male sex (Li et al., 2016). Moreover, it is known that women have a higher lifetime risk of developing AD and are also more likely to be diagnosed with it (Li & Singh, 2014; Nebel et al., 2018; Podcasy & Epperson, 2016). Nevertheless, women mostly get older than men, which leads to the assumption that women fall ill at a comparatively later age than men (Beam et al., 2018). In our sample, women and men were of a similar age, and analyses revealed male sex as a predictor for study dropout. In line with other research literature, we suggest that this effect may be explained due to earlier death or by sex-specific distinctions in cognitive domains such as lower performance of men in declarative memory (Haberstumpf et al., n.d.; Febo et al., 2020; Li & Singh, 2014; Muniz-Terrera et al., 2009; Nebel et al., 2018; Piccinin et al., 2013; Vega et al., 2010). Third, we saw that participants differed in educational level, but the educational level did not predict dropout behaviour at first follow-up as can be revealed by the different statistical procedures for the inclusion of the covariates in the MANCOVAs and regression analyses. We recommend study replications, as education level is also considered a promising predictor variable of cognitive decline and thus may also be relevant to long-term dropout behaviour (Sharp & Gatz, 2011; Xu et al., 2015).

In sum, this analysis found out that a possible confound between cognitive impairments and study dropout should be considered. If the goal in future analyses is to identify and separate corresponding effects, appropriate statistical methods might be helpful. For example, Levin et al. (2000) applied discriminant analysis to detect cognitive decline in neuropsychological measures as a predictor for study attrition in a sample of patients with

Parkinson's disease and possible dementia. Moreover, we suggest using such statistical methods that aim to control confounding variables, for example, randomization, matching of samples or the adjustment of confounding factors (Bernstein et al., 2021).

From a more practical few, it may be helpful to apply retention tactics to reduce dropout rates in long-term studies. Actual reviews describe the association between the employment of diverse retention techniques and retention rates (Robinson et al., 2007, 2015). We also tried to retain study participants in terms of the Vogel study. For instance, we provided study procedure information such as time schedules to all participants and educated them about follow-ups. Information events were provided. Our staff initiated contact regularly by phone and mail for new clinic appointments and informed them about findings and diagnoses. We tried to make adequate offers during the investigation appointments (e.g. drinks and food, regular breaks). Moreover, we tried to accommodate participants who were unable to come to the clinic themselves for an appointment, for example, due to illness, and visited them at home. All staff received regular and qualified training, were assigned to, and showed interest in the respective study participants. Because the clinic refunded parking tickets or postage fees, all study participants could be financially reimbursed.

Our study also had some limitations. First, despite a large sample size of participants in the Vogel study, individual subsamples differ partly extensively. Hence, individual statistical results should be interpreted with caution. Second, we had to exclude diverse groups of participants because of a lack of information (see Section 2). Due to this, it could be possible that we also lost some helpful information. Moreover, in analyses as ours, numerous covariates, confounding or informing participant variables such as the socio-economic status, transportation needs, and resources, support networks, motivations to participate in research and research attitudes could be included. For future analyses, it would be helpful to investigate more of them and ask the participants for them, for example, based on suitable questionnaires (Stites et al., 2021). Mainly since the onset of the corona pandemic in 2019 and associated contact restrictions, for example, lower social support and limitations in daily life are expected in our sample of elderly, which may have implications for cognitive decline and dropout rates. Third, we had some methodological issues. Testing the assumption of equality of covariance matrices using the Box's test for our MANCOVAs, we found highly significant results in all cases ($p < 0.01$). However, this small model accuracy can be explained by the model complexity. This finding is suggested usually in large samples producing greater (co-)variances (Tabachnick & Fidell, 2012). Therefore, probability values are more conservative, and significant results can be relied on. Furthermore, the log-likelihood based Cox and Snell's pseudo-R^2 for both models were relatively small ($R^2 = 0.09$ for cognitive performance factors, $R^2 = 0.08$ for autonomy in daily routine diagnostics). Converted into the effect size f, values of around 0.30 result. These numbers revealed a medium effect and is considered good (Cohen, 1992).

To sum up our research, we found out that the participant's performance in declarative memory, attention, visual–spatial processing and MMSE are predictors for study dropout. We extended the literature by paying attention to cognitive decline not only as a dependent variable but rather as a predictor for dropout behaviour in a longitudinal study. These findings may enable us to define new assumptions about the development of pathological cognitive deficits in research. Research should pay more attention to possible effects for subsequent results.

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AUTHOR CONTRIBUTIONS

Sophia Haberstumpf analysed the data and wrote the first draft of the publication. Jonas Leinweber, Martin Lauer and Thomas Polak were responsible for medical investigations and proficient supervision. Jürgen Deckert, Thomas Polak and Martin J. Herrmann were involved in study design and data acquisition. All authors critically revised the publication, made considerable suggestions and approved to the final script to be published.

CONFLICT OF INTERESTS

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PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data are available on request due to restrictions.

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