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Validation of the "Perceptions Regarding pRE-Symptomatic Alzheimer's Disease Screening" (PRE-ADS) Questionnaire in the German Population: Attitudes, Motivations, and Barriers to Pre-Symptomatic Dementia Screening

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Abstract.
Background: Attitudes, motivations, and barriers to pre-symptomatic screening for Alzheimer's disease (AD) in the general population are unclear, and validated measurement tools are lacking.
Objective: Translation and validation of the German version of the "Perceptions regarding pRE-symptomatic Alzheimer's Disease Screening" (PRE-ADS) questionnaire.
Methods: A convenience sample ($N = 256$) was recruited via an online platform. Validation of the PRE-ADS-D consisted of assessments of reliability, structural validity using Principal Component Analysis (PCA) and Exploratory Factor Analysis (EFA) and construct validity using known-group tests. A subscale "Acceptability of Screening", with 5 PRE-ADS-D items, was extracted to measure acceptance of screening in clinical practice. The STROBE checklist was used for reporting.
Results: EFA revealed a three-factor model for the PRE-ADS-D. Acceptable to good internal consistency was found for the 25-item scale ($\alpha = 0.78$), as well as for the three factors "Concerns about Screening" ($\alpha = 0.85$), "Intention to be Screened" ($\alpha = 0.87$), and "Preventive Health Behaviors" ($\alpha = 0.81$). Construct validity was confirmed for both the 25-item PRE-ADS-D and the "Acceptability of Screening" scale ($\alpha = 0.91$). Overall, 51.2% of the participants showed a preference for screening. Non-parametric tests were conducted to further explore group differences of the sample.
Conclusions: The PRE-ADS-D is a reliable and valid tool to measure attitudes, motives, and barriers regarding pre-symptomatic dementia screening in the German-speaking general population. Additionally, the subscale "Acceptability of Screening" demonstrated good construct validity and reliability, suggesting its promising potential as a practical tool in clinical practice.

Keywords: Alzheimer's disease, attitude, biomarker, psychometrics, screening, validity

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INTRODUCTION

Dementia, the seventh leading cause of mortality, affects over 55 million people worldwide [1] and is one of the most feared diseases [2]. Nearly 10 million new cases are recorded annually, although it is estimated that 75% of people with dementia (PwD) are undiagnosed at death, and up to 90% in some low- and middle-income countries [1]. As research has shown, routine screening could lead to a higher diagnosis rate, and early treatment may at least partially delay cognitive decline [3, 4], advances in dementia diagnosis have led to an increasing number of studies on the acceptability of early dementia screening [5–12] in older adults, but there is a paucity of data examining community attitudes toward pre-symptomatic screening.

The discovery of biomarkers associated with the pathophysiology of Alzheimer's disease (AD) [13] has led to a paradigm shift from a clinical diagnosis based on functioning to a biological diagnosis based on biomarkers and PET [14] and to a new understanding of dementia as a continuum [15, 16]. The pathophysiological process begins decades before the first symptoms become clinically apparent [17], in a preclinical, asymptomatic stage, in which there is biomarker evidence of AD pathology, followed by a prodromal stage of mild cognitive decline with neuropathological changes typical of AD [15]. Therefore, biomarkers and genetic susceptibility screening are gaining increasing attention in health care, research, and direct-to-consumer (DTC) settings [18–20].

The utility of biomarkers such as noninvasive neuroimaging, cerebrospinal fluid (CSF), containing $A\beta_{1-42}$, $A\beta_{1-40}$, tau, phospho-tau, and neurofilament light chain (NfL), and genetic risk factors of AD is controversial because of limited prognostic value [21, 22], and because pre-symptomatic screening is without therapeutic consequences as long as safe treatment options are not available. In addition, it may also harm asymptomatic individuals through ineffective overdiagnosis and overtreatment [23]. The clinical validity of both CSF biomarkers and "amyloid PET positivity" is intensely investigated. The problem is that not all individuals with positive biomarkers or amyloid PET will become symptomatic [24]. Although biomarkers for AD may have an undeniable value for research, the benefit of pre-symptomatic screening appears limited [25].

Since the discovery of the Aβ-encoding APP gene in 1987 [26], developments in AD genetics have led to the identification of four genes involved in AD [27]. Three are known deterministic genes in which mutations are associated with early-onset autosomal dominant AD (EOAD) before the age of 60–65 years, accounting for 1–5% of all AD cases [28] and approximately 80% of EOAD cases [29]: the amyloid precursor protein (*APP*) on chromosome 21 [30], presenelin 1 (*PSEN1*) on chromosome 14 [31], and presenelin 2 (*PSEN2*) on chromosome 1. Recently, SORL1 has been identified as the fourth familial, sometimes even autosomal-dominant, AD gene. It is estimated that potentially damaging *SORL1* variants affect as many as 2.75% of all unrelated people with early-onset AD, and 1.5 percent of those with late-onset AD (LOAD) [32].

For LOAD, genome-wide association studies (GWAS) have shown that many genetic loci contribute to AD risk [33], while apolipoprotein E (*APOE*), with its isoform ε4 (*APOE4*) on chromosome 19 appears to be the major susceptibility gene [28]. While the ε2 allele plays a protective role [34], *APOE4* increases the risk in a dose-dependent manner: A single ε4 allele increases the risk of AD approximately threefold, while homozygotes have a 15–30-fold increased risk [35]. However, these susceptibility genes are only associated with an increased risk for the disease development, while many other (environmental) factors play a role in whether the disease is manifested, in contrast to familial AD or Huntington's disease, where genetic tests have a predictive value of clinical relevance [36].

While biomarkers and genetic testing may be useful in clarifying a clinical diagnosis, the question of their utility in asymptomatic individuals arises in the absence of effective therapy and despite the paucity of evidence for biomarkers and amyloid scans [23, 37], as well as despite the lack of sensitivity and specificity of the biomarkers and their unclear predictive ability [14]. A biomarker must have a sensitivity of at least 90%, a specificity approaching 100%, a high degree of reliability, and the ability to detect one or more fundamental features of the relevant neuropathologic changes. These requirements are not met by imaging markers or by *APOE4* [38, 39]. Biomarker data are limited in asymptomatic individuals but suggest that abnormal biomarkers are common and not indicative of dementia in the majority of individuals [40] and add only little value in predicting whether a person will develop dementia in the next few years [41]. Because of the uncertainty of biomarker results [42, 43], it is questionable whether a condition with abnormal biomarkers should be considered a dis-

ease or an at-risk condition in the absence of clinical symptoms [14]. Therefore, even testing for *APOE4* is not recommended in asymptomatic individuals [28, 44]. In addition, testing asymptomatic individuals for dementia raises ethical questions about the appropriateness of using biomarkers or genetic tests and about the personal benefits of pre-symptomatic testing. The basic principles of bioethics—autonomy, beneficence, non-maleficence, and justice [45]—can help to identify moral values in the debate about the ethical desirability of pre-symptomatic screening for AD. Respect for autonomy emphasizes the importance of a person's knowing or not knowing what is going on in their brain and their risk status for AD [25, 21]. This requires that the person understands what to expect and that the person understands the uncertainty of the results. The benefits of pre-symptomatic screening must always outweigh the risk of harms related to discrimination, overdiagnosis, and psychological harm, as well as the burden and risk of testing itself [25]. Other harms include irreversible decisions, changes in self-perception, family disruption, especially when hereditary risk factors may be involved [24], internalized stigma (how individuals feel about themselves) and public stigma (how others judge them) [25], as well as political questions about voting, driving, and economic questions about balancing an employer's right to a productive workforce with an employee's right to avoid discrimination on the basis of dementia risk [26], leading to a dilemma between privacy, protection, and family responsibilities [46].

Benefits are often based on misconceptions and unrealistic expectations [14], such as better planning for the future, improved health and well-being, adoption of a healthier lifestyle, as well as a desire to better understand their brain health status [47]. According to Erdmann et al. (2018), the benefits outweigh the harms only among people with symptoms who seek support [48]. Although the benefit of knowing the risk of AD is currently questionable, it may be of great benefit in the near future once therapy is available [4, 49]. Finally, justice concerns the limited availability of biomarker and genetic testing but also the risk of discrimination based on an AD diagnosis [25].

The motives for pre-symptomatic screening are not always clear. They may be intrinsically motivated, or they may be driven by fear or hope of preventing AD. This hope makes them vulnerable to misconceptions and unrealistic expectations [14]. Arguments for testing include people's right to know (or not know) their risk, to plan and prepare for the future, both financially and emotionally, to spend more time with family, to purchase long-term care insurance, and to support basic research [18, 50–52]. As long as the prognostic value is unclear and the risk prediction inaccurate, this argument has only a limited validity [24]. Labeling large numbers of asymptomatic people with pre-symptomatic dementia or at risk without being sure they will develop symptoms seems to have little or no benefit and creates a group of "patients in waiting" [14]. There is also the risk of medicalization [53], as unnecessary tests and treatments can also have side effects [23, 54], adverse psychological and social outcomes [14], and require financial resources that are needed elsewhere. The often-heard argument that it is possible to change one's lifestyle with knowledge of a risk is not really convincing as it is possible—and even desirable in terms of a healthier lifestyle—to change one's lifestyle without knowledge of a risk [55]. But once a person is labeled with a pre-disease, he or she will remain so for life [56]. In the case of genetic testing, this also has implications for the family since genes, strictly speaking, affect not only the person tested but the entire family [57].

With the ever-increasing number of biomarkers and the ability to test outside of clinical trials using the DTC genetic testing, the question arises regarding the attitudes, motivations, and barriers to pre-symptomatic testing in the general population. Previous studies have focused on the attitudes, knowledge needs, benefits and barriers to dementia screening of a specific population, mostly relatives of PwD [52], using self-administered survey questionnaires or structured interviews [18, 58–61]. Validated scales include the "Perceptions Regarding Investigational Screening for Memory in Primary Care" (PRISM-PC) [7], which assesses attitudes toward dementia screening in primary care, and the "Dementia Screening and Perceived Harms" (SAPH) [11, 62], which assesses the acceptability of dementia screening in primary care. As these scales were developed to investigate the acceptability of early dementia screening, but not necessarily for pre-symptomatic screening, and lack questions about the need for knowledge or the type of support that people would like to receive before, during, and after the disclosure of the test results, Makri et al. (2023) [63] developed the "Perceptions regarding pRE-symptomatic Alzheimer's Disease Screening" (PRE-ADS) questionnaire [63], which was based on the PRISM-PC [7], a literature review and a panel of clinical experts from the Greek Association for Alzheimer's Disease

and Related Disorders (GAADRD). The scale would be helpful for further research into ethical implications, knowledge of the sensitivity and validity of biomarker and genetic tests, their benefits and limitations, and exploration of cultural differences.

The aim of this cross-sectional study was a) to examine the psychometric properties of the German version of the PRE-ADS in the general population and b) to examine the psychometric properties of the subscale, "Acceptability of Screening". In addition, we aimed to further investigate potential influences on participants' attitudes, motivations, barriers, and acceptability of screening based on their demographic background or personal experience with dementia.

MATERIALS AND METHODS

Study design

This is a cross-sectional study to evaluate the psychometric properties of the German version of the PRE-ADS (PRE-ADS-D). The "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) checklist [64] was used in accordance with the EQUATOR guidelines for research reporting (Supplementary Material 1).

Participants

Between May and July 2022, a convenience sample was recruited through newsletters, flyer distribution, and by forwarding the call to participate in the study via WhatsApp and Facebook. Inclusion criteria were age over 18 years and a high German language proficiency. According to the rule of thumb that at least 10 people per item are needed [65], a sample size of 250 (25*10) was required. The final sample size was $N = 256$.

Data collection procedure

A structured questionnaire (Supplementary Material 2) was prepared, covering socio-demographics (age, gender, marital status, education level, occupation), mental and physical health status, as well as prior experiences with dementia, such as caregiving for PwD, having a positive family history (affected family members along with the extent of their relationship), having engaged in a dementia program previously, or having undergone prior dementia screening, followed by the 25 questions of the PRE-ADS-D questionnaire. Participants completed the survey online via Google Forms using a link or QR code. Participants took approximately 5–10 min to complete the questionnaire.

"Perceptions regarding pRE-symptomatic Alzheimer's Disease Screening" (PRE-ADS)–a 25-item questionnaire

PRE-ADS was developed to measure attitudes, motivations, and barriers regarding pre-symptomatic screening for dementia [63]. The original Greek version was validated with a mixed group of university students and informal carers for PwD. The instrument consists of 25 items on a five-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). The total scores achievable for this scale range from 25 to 125, with a higher score indicating greater agreement with the acceptability of pre-symptomatic screening for AD and the perceived benefits of screening, greater need for knowledge about AD risk, and less perceived harm. Ten items were reverse scored (9, 10, 11, 12, 15, 16, 18, 19, 20, 21). In the Greek sample, PRE-ADS has a four-factor structure with a robust internal consistency ($\alpha = 0.82$). The first factor ($\alpha = 0.87$) is labeled as "Perceived Harms of Testing" (items 9, 10, 11, 12, 15, 16, 18, 19, 20, 21), the second factor ($\alpha = 0.85$) "Acceptance of Testing" (items 1, 2, 3, 4, 5), the third factor ($\alpha = 0.76$) "Perceived Benefits of Testing" (items 13, 17, 22, 23, 24, 25), and the fourth factor ($\alpha = 0.70$) "Need for Knowledge" (items 6, 7, 8, 14).

Developing the German version of the PRE-ADS

The translation-back translation method [66] was used to translate the English version of the PRE-ADS. Specifically, two German experts in dementia studies separately translated the English version into German. The translations were checked by the research team to resolve differences and, in case of discrepancies, the Greek version was consulted. The synthesis of the two translations was back-translated by a bilingual, native English-speaking public health expert and an English-German translator. The back-translated version was compared with the original English version for consistency, relevance, and meaning of the content. The scales were administered to five individuals to identify potential comprehension difficulties.

Statistical analysis

Descriptive and inferential statistical analyses were performed using SPSS V27.0. The Kolmogorov-Smirnov test was used to test the sample's mean score variable for normal distribution ($p < 0.05$). The following psychometric properties were assessed: internal consistency, structural validity, and known-group validity. Internal consistency reliability reflects how well a test addresses different constructs and provides reliable scores [67]. The interconnectedness of items is measured by Cronbach's alpha coefficient, which ranges from 0 to 1. A value between 0.70 and 0.95 indicates a high level of internal consistency, and values above 0.95 indicate redundancy of items.

Structural validity, defined as the extent to which the scores of a questionnaire adequately reflect the dimensionality of the construct being measured [68], was primarily examined using exploratory factor analysis (EFA). Prior to the EFA, a principal component analysis (PCA) with varimax rotation was performed as an initial exploration of the data structure. To test whether the variables were suitable for PCA, the Kaiser-Meyer-Olkin (KMO) value was calculated for sample adequacy (minimum acceptable value is 0.50), and Bartlett's test of sphericity was calculated to determine the suitability of the scale items for analysis (should be significant with $p < 0.05$). EFA was then used to identify latent factors in the data-. To reconstruct a lower dimensional dataset that still included adequate sources of variance, the Guttman-Kaiser eigenvalue-greater-than-one rule was applied, and the results were confirmed using a scree plot [69]. Kendall's Tau correlation was used to assess the relationship between the factors.

Known-group tests were used to examine the construct validity of the 25-item PRE-ADS-D. We hypothesized that age, personal experience, or having more knowledge about dementia could possibly influence a person's attitudes, motives, and barriers related to pre-symptomatic AD screening. T-tests were used to determine whether the questionnaire could accurately differentiate between younger and older participants (under and over 65), those with or without a family member with dementia, and those who had or had not attended a dementia education course. We hypothesized that: 1) there will be a significant difference in mean PRE-ADS-D scores between younger (< 65 years) and older (≥ 65 years) participants; 2) there will be a significant difference in the PRE-ADS-D mean score between participants with personal experience of dementia within the family and those without such experience; and 3) there will be a significant difference in the PRE-ADS-D mean score between individuals who have attended a dementia course or training and those who have not. Information on these characteristics was explicitly requested in the introductory part of the questionnaire (Supplementary Material 2). Age was stratified into two groups: those younger than 65 years (ranging from 18 to 64) and those older than 65 years (ranging from 65 to 99) [70, 71]. The two-sample *t*-test was used to test the hypotheses. This parametric test was chosen because it is suitable for comparing the means of two independent groups with respect to the continuous outcome variable, mean score, which follows a normal distribution [70, 71]. Effect sizes for the *t*-test were calculated using Cohen's d, which measures the standardized difference between the means of the two groups and provides an indication of the practical significance of the observed difference [71, 72].

"Acceptability of Screening"–a 5-item subscale

In order to be able to make specific statements about the subjects' acceptance of pre-symptomatic dementia screening, a smaller scale was extracted from the entire questionnaire, following the approach of Braun and colleagues (2014) [12]. These specific items focus on assessing participants' inclination to find out if they are at higher risk of dementia (item 1) and their willingness to undergo routine testing for dementia risk or presence using various diagnostic procedures (items 2, 3, 4, 5) (Table 2; Supplementary Material 2). The mean score for this scale was calculated by summing all of the responses given by each participant for the five items. This sum was then divided by the number of items to obtain an average score. This calculation was conducted using the "compute variable" function in SPSS 27.0. Therefore, a higher score on this mini-scale indicates a greater level of agreement and acceptance toward routinely pre-symptomatic and diagnostic AD screening.

Following Braun et al. (2014) [12], the acceptance score was recoded into a dummy variable with the values 0 "no acceptance" and 1 "acceptance". Values between 1.0 and 3.0 were recoded to 0, while higher values from 3.1 to 5.0 were transformed to 1. The purpose of this procedure was to create a variable that distinguished between acceptance and non-acceptance of screening. This allowed us to make

descriptive, percentage-based observations about the overall acceptability of the sample as a whole or based on different grouping variables.

Internal consistency by Cronbach's alpha coefficient as well as construct validity through known-group analyses were examined for the subscale "Acceptability of Screening", using the same hypotheses as for the PRE-ADS-D. The non-parametric Wilcoxon-Mann-Whitney test (WMW) was used to test these hypotheses, as the outcome variable was not normally distributed [73]. Additional two-sample Kolmogorov-Smirnov tests were performed to assess the variance homogeneity of the groups [71, 74].

Ethics

The study protocol was approved by the Ethics Committee of the Faculty of Behavioral and Cultural Studies, University of Heidelberg, Germany (AZ Tei2022 1/2). All procedures involved in this work conformed to the ethical standards of the Declaration of Helsinki, as applicable to national and institutional human experimentation committees. All participants participated voluntarily in the study. They were informed about the procedure and the aim of the study and then gave their consent to participate via an informed consent option in the online questionnaire.

RESULTS

Participants' characteristics

Sociodemographic characteristics, participants' experience with AD, previous dementia programs, concern about AD diagnosis, and belief in dementia treatment of the 256 participants are shown in Table 1. In summary, the main characteristics were as following: the mean age was 45.83 years (18–99 years), most participants were female (69.1%), with more than 13 years of education (69.9%), 17.2% had a medical profession (e.g., physicians, therapists, or other medical occupations), 70.3% knew at least one person with dementia, and most participants had never attended a course or seminar on dementia (69.9%). Most participants were not worried about getting dementia (60.2%), and 41.4% believed there would be an effective dementia therapy in the next five years.

PRE-ADS-D

Structural validity

The KMO measure of sampling adequacy was 0.819, indicating that the sampling is adequate with a good internal consistency without too much item redundancy. Bartlett's sphericity test was found to be significant ($\chi^2(256) = 3348.24$, $p < 0.001$). Thus, the sample consisted of related variables, and the requirements for the EFA were met. First, a PCA with varimax rotation was performed. With an eigenvalue of at least 1 and with the criterion for factor loading of 0.30, a six-factor solution was obtained with an explained variance of 65.85%. Eight items loaded on the first factor, five on the second, five on the third, three on the fourth, two on the fifth, and two on the sixth. Due to the lack of a clear structural form with five items loading on two factors, a scree test was considered, which showed a clear three-factor solution. A three-factor EFA was performed, which explained 49.66% of the total variance. Three items still loaded on two factors (cross-loadings), with two of them (items 7 and 13) showing a clear preference for factor 3, while item 8 did not exhibit a clear preference between Factors 2 and 3. After taking into consideration theoretical and practical implications, item 8 was included in factor 3. The ten reverse-scored items all loaded on the first factor labeled "Concerns about Screening", 6 items loaded on the second factor "Intention to be Screened," while 9 items loaded on the third factor "Preventive Health Behaviors" (Table 2).

Internal consistency

The internal consistency of the 25-item scale was $\alpha = 0.78$, indicating good interrelatedness among the items. The internal consistency of each factor separately was also very satisfactory. Specifically, the reliability of factor 1 ("Concerns about Screening") was $\alpha = 0.85$, that of factor 2 ("Intention to be Screened") was $\alpha = 0.87$, and that of factor 3 ("Preventive Health Behaviors") was $\alpha = 0.81$. Only two items would increase the Cronbach's alpha value if deleted: For factor 2, the value of Cronbach's alpha would increase from 0.87 to 0.91 if item 6 were removed. If item 17 were removed from factor 3, the value would increase from 0.81 to 0.82 (Table 2). However, as the PRE-ADS-D will be used in future comparative studies alongside the original Greek version and three other translated versions (Spanish, Turkish, Belgian Dutch), we decided not to remove or modify any items from

Table 1
Demographic characteristics of the survey sample ($N = 256$)

Characteristics			
Age mean (SD)	45.83 (18.20)	*n*	%
Age Groups			
18–35		90	35.2%
35–65		133	52.0%
65–80		27	10.5%
80+		6	2.3%
Gender			
Male		79	30.9%
Female		177	69.1%
Education level			
0–9 years		3	1.2%
9–13 years		74	28.9%
>13 years		179	69.9%
Occupation			
Physician		7	2.7%
Care Profession		5	2.0%
Therapeutical Profession		25	9.8%
Other Medical Professions		7	2.7%
Student		59	23.0%
Retiree		35	13.7%
Other		118	46.1%
Experience with PwD			
No experience with PwD		76	29.7%
I know one or more PwD		180	70.3%
First-degree relative affected		101	39.5%
I care for a PwD		13	5.1%
Participation in program about dementia			
Yes		77	30.1%
No		179	69.9%
Worried I will get dementia			
I am not worried		154	60.2%
I have some memory problems		30	11.7%
I have a higher risk/worried		72	28.1%
Believe there is an effective dementia treatment			
Yes/There will be in 5 years		106	41.4%
No		84	32.8%
I don't know		66	25.8%

the questionnaire in this study in order to develop comparable instruments for further analyses. The Kendall-Tau correlations between Factor 1 ("Concerns about Screening") and Factor 2 ("Intention to be Screened") ($\tau(254) = -0.074$, $p = 0.09$) and Factor 3 ("Preventive Health Behaviors") ($\tau(254) = -0.071$, $p = 0.11$) were weak and not significant. Factor 2 ("Intention to be Screened") and factor 3 ("Preventive Health Behaviors") were strongly positively correlated ($\tau(254) = 0.331$, $p < 0.001$).

Construct validity

The results for all known-group tests are shown in Table 3. An independent samples t-test revealed that the PRE-ADS-D can accurately differentiate between older (≥ 65 years) and younger participants (< 65 years) ($t(254) = 2.216$, Cohen's $d = 0.41$, $p < 0.05$). The mean score regarding the 25-item PRE-ADS among older adults ($n = 33$) ($M = 81.18$, $SD = 9.75$) was significantly higher than that of the younger adults of the sample ($n = 223$) ($M = 77.05$, $SD = 10.02$) with a small to moderate effect size (Cohen's $d = 0.41$) [71, 72]. This confirms our first hypothesis that the PRE-ADS-D mean score would differ significantly between older and younger adults, whereas hypotheses two and three could not be confirmed ($p > 0.05$).

Additional analyses investigating group differences

Additional group comparisons are depicted in Table 4. Analyses confirmed that the PRE-ADS-D mean score was statistically different between younger and older adults (under and over the age of 65). In order to gain a deeper understanding of the reasons behind this result, we conducted addi-

Table 2
Exploratory factor analysis of the PRE-ADS-D

Nr.	Item "If I was informed that I am at a higher risk of AD . . . "	Mean (SD)*	Cronbach's α if item deleted	Factor 1	Factor 2	Factor 3
11.**	I feel that I would be overwhelmed by mental pain.	2.64 (0.94)	0.83	**0.78**		
12.**	I feel that I would be overwhelmed by intense anxiety.	2.49 (0.96)	0.83	**0.76**		
19.**	I would be depressed.	2.34 (0.93)	0.83	**0.73**		
20.**	I would be anxious.	2.37 (0.97)	0.83	**0.72**		
16.**	My family would suffer emotionally.	1.91 (0.84)	0.83	**0.72**		
10.**	My family will suffer emotionally.	1.69 (0.82)	0.83	**0.69**		
15.**	My family would suffer financially.	2.75 (1.07)	0.84	**0.58**		
21.**	I would give up on life.	3.91 (0.86)	0.85	**0.54**		
09.**	My family will suffer from the additional costs of my care.	2.60 (1.15)	0.85	**0.51**		
18.**	I think that others will treat me in a different way.	2.41 (0.87)	0.85	**0.50**		
03.	I would like to be tested for the presence of AD on a regular basis with a blood sample.	3.24 (1.27)	0.83		**0.84**	
01.	I would like to know if I am at higher risk than others for developing Alzheimer's disease.	3.54 (1.19)	0.80		**0.81**	
04.	I would like to be tested for the presence of AD on a regular basis with pictures of my head or brain (CT scan or MRI).	2.75 (1.18)	0.84		**0.81**	
05.	I would like to be tested for the presence of AD on a regular basis with the use of biomarkers in cerebrospinal fluid (Aβ amyloid, t-protein).	2.72 (1.11)	0.84		**0.80**	
02.	I would like to be tested for the presence of AD on a regular basis with a short questionnaire.	3.34 (1.21)	0.84		**0.79**	
06.	In order to decide to be tested for the presence of AD, I would need more information and details.	3.65 (1.23)	0.91		**0.40**	
23.	I would have more time to talk with my family about my health care.	3.57 (0.92)	0.78			**0.82**
24.	I would have more time to talk with my family about my finances.	3.49 (0.93)	0.78			**0.78**
22.	I would have more time to plan my future.	3.11 (0.97)	0.80			**0.65**
25.	I would be motivated to have a healthier lifestyle (physical exercise, diet, vitamins, cognitive stimulation, stop smoking).	3.89 (0.96)	0.80			**0.59**
14.	I will be motivated to stay abreast of new developments in AD treatment and prevention.	4.28 (0.82)	079			**0.57**
13.	I would improve my quality of life.	3.50 (0.98)	0.80		0.30	**0.52**
07.	I would like to discuss it further and to get advice from a doctor or another health professional expert in this field.	4.46 (0.82)	0.79		0.38	**0.52**
17.	My family would have a better chance to take care of me.	3.00 (0.82)	0.82			**0.39**
08.	I would like to meet a health professional, expert on genetics, in order to discuss my feelings and my thoughts.	3.94 (1.10)	0.81		0.36	**0.38**
	Eigenvalueλ of the rotated factors			4.53	4.14	3.75
	Total variance explained Σ 49.66%			**18.12%**	**16.54%**	**15.00%**

*Mean score of answers according to a Likert Scale (1 = I totally disagree, 2 = I disagree, 3 = I don't know, 4 = I agree, 5 = I totally agree). **Reversed-scored items (1 = I totally agree, 2 = I agree, 3 = I don't know, 4 = I disagree, 5 = I totally disagree).

Table 3
Known-Group-Tests for construct validity of the PRE-ADS-D – Results of the *t*-tests

Age Groups	Under 65 years ($n = 223$)	65 years and older ($n = 33$)	t[1]	Cohen's d[2]	P[3]
mean score M	81.182	77.054	2.216	0.413	**<0.05**
Affected Family Member	Yes ($n = 101$)	No ($n = 155$)	*t*	d	*p*
mean score M	78.584	76.935	1.283	0.164	>0.05
Participated in dementia training	Yes ($n = 77$)	No ($n = 179$)	t	d	*p*
mean score M	76.558	78.028	–1.072	–0.146	>0.05

[1]t = *t*-value, *t*-test statistic, [2]Cohen's d = value for measuring effect size, [3]*p* = significance.

Table 4
Additional Group comparisons

Age Groups	Under 65 ($n = 223$)	Over 65 ($n = 33$)	U[1]	z[2]	P[3]	K-S test[4]
Factor 1 "Concerns about Screening", mean rank	122.99	165.73	2451.0	–3.099	**<0.01**	<0.05
Factor 3 "Preventive Health Behaviors", mean rank	128.67	127.32	3640.5	–0.098	0.922	>0.05

[1]U, *U* test statistic; [2]z, z statistic; [3]*p*, significance; [4]K-S test, two-sample Kolmogorov-Smirnov test for variance homogeneity.

tional WMW tests with the different factors resulting from the EFA as dependent variables. This was done because these factors play a crucial role in structuring and reflecting the content of the questionnaire. As stated above, the results of the EFA showed a three-factor model for the PRE-ADS-D questionnaire. Factor 1 assessed "Concerns about Screening", Factor 2 assessed "Intention to be Screened", and Factor 3 assessed "Preventive Health Behaviors". As Factor 2, "Intention to be Screened" (items 1, 2, 3, 4, 5, 6), was very similar to our subscale "Acceptability of Screening" (items 1, 2, 3, 4, 5), it was excluded from the analyses. The dichotomized age variable was used as the grouping variable, while the mean scores of Factors 1 and 3 were used as outcome variables. WMW tests revealed a statistically significant difference between age and the mean score of Factor 1 "Concerns about Screening" ($U(254) = 2451.0$, $z = -3.099$, $p < 0.01$).

"Acceptability of Screening" - a 5-item subscale

Calculation of this subscale yielded a mean acceptance score for the entire sample ($N = 256$, $M = 3.12$, $SD = 1.02$) with values ranging from 1.0 to 5.0 (median = 3.2) and a slightly negatively skewed distribution (–0.181). Considering the skewness, median, mean, and standard deviation, the distribution of the variable "Acceptability of Screening" appears to be relatively symmetric, and the overall tendency of the sample tends toward "neutral" or "slightly agree".

A dummy variable was recoded following the procedure outlined by Braun et al. (2014) [12]. Overall, 131 participants (51.2%) expressed their support for routine pre-symptomatic and diagnostic screening for screening, while 125 participants (48.8%) indicated that they would not accept routine screening. When considering only the participants from a sample with a family member with dementia ($n = 101$), the acceptability of screening increases to 57.4% ($n = 58$), while 42.6% ($n = 43$) do not accept screening. On the other hand, for respondents without an affected family member ($n = 155$), the acceptance rate is 47.1% ($n = 73$). Looking at the age groups, we found that 66.7% of participants aged 65 years and older were willing to accept routine AD screening. On the other hand, among adults under 65 years, less than half (48.9%) would be willing to accept the routine AD screening. Finally, only about a third (36.4%) of the participants who had received dementia training expressed a positive attitude toward screening. In contrast, among the participants without dementia training, a higher number of individuals (57.5%) indicated that they would accept such dementia screening.

Internal consistency

Cronbach's alpha for the mini-scale was $\alpha = 0.91$, indicating excellent internal consistency [75]. This not only ensures its reliability but also confirms the unidimensionality of the scale, as high item intercorrelations (or high internal consistency) are only possible when the individual items are minimally affected by random measurement error [71].

Table 5
Known-Group Tests for construct validity of the mini scale "Acceptability of Screening" – Results of the Wilcoxon-Mann-Whitney tests

Age Groups	Under 65 years ($n = 223$)	65 years and older ($n = 33$)	U[1]	z[2]	P[3]	K-S test[4]
"Acceptability of Screening" subscale, mean rank	125.94	145.77	3109.5	–1.439	>0.05	>0.05
Affected Family Member	Yes ($n = 101$)	No ($n = 155$)	U	z	p	K-S test
"Acceptability of Screening" subscale, mean rank	141.66	119.93	6498.5	–2.300	**<0.05**	<0.05
Participated in dementia training	Yes ($n = 77$)	No ($n = 179$)	U	z	p	K-S test
"Acceptability of Screening" subscale, mean rank	109.03	136.88	5392.0	–2.766	**<0.05**	<0.05

[1]U = U test statistic, [2]z = z statistic, [3]p = significance, [4]K-S test = two-sample Kolmogorov-Smirnov test for variance homogeneity.

Construct validity

Known-group tests for the subscale "Acceptability of Screening" are demonstrated in Table 5. Two of our three initial hypotheses were confirmed: WMW Tests revealed significant differences in the mean score of the subscale "Acceptability of Screening" (2) between participants with personal experience of dementia within the family and those without such experience ($U(254) = 6498.500$, $z = -2.300$, $p < 0.05$) and (3) between individuals who have participated in dementia courses or training than those who have not received any training ($U(254) = 5392.0$, $z = -2.766$, $p < 0.01$). Therefore, the mean scores of the subscale "Acceptability of Screening" were significantly different between individuals with or without an affected family member and with or without participation in a dementia course.

Finally, an additional chi-square test was conducted to explore whether there was a significant difference regarding the fear of developing dementia between participants with an affected family member and those without. The results revealed that the presence of a family history of dementia is significantly linked with an increased concern about the risk of developing dementia ($\chi^2 = 60.72$, $df = 3$, $p < 0.001$) with a Cramér's V (phi) of 0.488, indicating a moderately strong association [71, 76, 77].

DISCUSSION

The aim of this cross-sectional study was to analyze the psychometric properties of the German version of the PRE-ADS in the general population. The questionnaire was practical for online administration in less than 10 min. Both the 25-item scale and its three factors, "Concerns about Screening", "Intention to be Screened", and "Preventive Health Behaviors", showed acceptable to good internal consistency. The PRE-ADS-D discriminates clearly between younger and older adults, but not between participants with and without affected family members or between those who have received dementia training and those who have not. The 5-item subscale "Acceptability of Screening" revealed that 51.2% of all participants expressed a positive attitude towards their willingness to undergo a pre-symptomatic or diagnostic AD screening. Internal consistency for this subscale was excellent. The subscale did not discriminate between younger and older people but showed a tendency to a higher acceptance of those over 65 years and discriminated between those with and those without a family history of dementia as well as between those who had attended a dementia course and those who had not. In addition, a significant association was observed between the fear of developing dementia and the presence of a family member with dementia.

The internal consistency is comparable with earlier reports of the original Greek version of the PRE-ADS [63] and to scales that focus on dementia screening, such as the PRISM-PC or modified scales [7, 10–12, 78, 79].

We found the strongest evidence for a three-factor structure for the PRE-ADS-D, in contrast to the study by Makri et al. (2023), which reported the four factors "Perceived Harms of Testing", "Acceptance of Testing", "Perceived Benefits of Testing", and "Need for Knowledge" [63]. However, when we looked closely at the items that loaded on each factor, we found that 21 out of the 25 items loaded on their intended factor, with the remaining four items forming the fourth factor in the original study, "Need for Knowledge" (items 6, 7, 8, 14). It is noticeable that these items either show lower factor loadings (0.38–0.57) or cross-loadings on other factors. Similar studies that are based on the PRISM-PC by Boustani et al. (2008) [7] have also shown slightly different results

in terms of the number of factors compared to the original proposal by its creators [11, 12]. Differences in factor loadings and model structure may be attributed to variations in sample characteristics [12]. In contrast to the predominantly student-based sample in Makri et al. (2023) [63], the sample in our study represents a more diverse range of the general German population: Participants in this study ranged in age from 18 to 99 years and had a variety of sociodemographic characteristics, including different occupations, education levels, marital status, family history of dementia, and different health and mental health status. In addition, attitudes, motivation, and barriers toward pre-symptomatic AD screening can differ across different countries due to culture-specific factors and variations in healthcare systems, as observed in dementia screenings in general [12, 80].

The first factor "Concerns about Screening" consists of 10 reverse-coded items that express participants' concerns if they knew they were at high risk for developing dementia (items 9, 10, 11, 12, 15, 16, 18, 19, 20, 21) and corresponds exactly to the factor "Perceived Harms of Testing" of Makri et al. (2023) [63]. These concerns can be categorized into individual psychosocial effects, such as emotional suffering (anxiety and depression) or stigma (items 11, 12, 18, 19, 20, 21), and family burden (emotional and financial) (items 9, 10, 15, 16). Examples include item 11 ("I feel that I would be overwhelmed by mental pain") and item 15 ("My family would suffer financially"). These findings align with the results of the other studies that utilized the PRISM-PS scale where similar items were included in the "Perceived Harms and Benefits of Testing" scale, and similar factors were identified as harms of testing, such as "stigma", "(emotional) suffering", "family burden", and "negative impact of screening on independence" [7, 12, 80]. It is well known that pre-symptomatic testing for any type of disease can indeed carry several risks, including discrimination, over-diagnosis, internalized stigma (individuals' self-perception), public stigma (how others perceive them), as well as political and economic considerations [27–29]. Since the benefits of genetic testing in asymptomatic individuals should always outweigh the potential concerns and harms, it is critical to identify the potential harms of AD screening and assess their perceived importance in order to incorporate them into future counseling programs [25, 80].

The second factor, "Intention to be Screened", incorporates all questions that assess the participants' preference to find out if they have a higher risk of dementia (item 1) or the willingness to be regularly tested for the presence or the risk of dementia by different screening methods such as regular completion of a questionnaire (item 2), blood sampling (item 3), imaging procedures (item 4), or biomarker screening (item 5). It also includes item 6 ("In order to decide to be tested for the presence of AD, I would need more information and details") (Table 2). Here, the results differ from those of Makri et al. (2023) [63], where items 1 to 5 load on the second factor, but item 6 loads on factor 4 ("Need for Knowledge"). In the present study, the inclusion of item 6 in the "Intention to be Screened" factor highlights the relationship between an individual's level of information about pre-symptomatic and diagnostic dementia screening and their attitudes toward screening. Prior knowledge plays an important role in shaping an individual's intention to undergo screening. This finding is consistent with the basic concepts and primary goals of genetic counseling, in which the provision of understandable, non-directive information is critical for the counselee to have sufficient knowledge in order to facilitate informed consent and to make an autonomous decision to undergo testing [81].

The remaining 9 items loaded on the third factor, "Preventive Health Behaviors" (Table 2). Early detection of one's predisposition may lead to the adoption of a healthier lifestyle (items 13 and 25) and may also allow individuals to have more time for overall processing, discussion, and planning for the future with family members. This includes discussing health issues, long-term care services, and financial planning (items 17, 22, 23, and 24).

In contrast to Makri et al.'s (2023) [63] third factor, "Perceived Benefits of Testing", our study's third factor, also included items 7, 8, and 14. Participants indicated that if they theoretically received a positive test result, they would seek counseling to gather advice in general (item 7), cope better psychologically or discuss their feelings and thoughts (item 8), and learn about prevention and treatment options (item 14). Interestingly, these remaining 3 items were added to the PRISM-PC by Makri et al. (2023) [63] and, together with item 6, contributed to the formation of the fourth factor in their validation study, called "Need for Knowledge". In the German study, these items seem to focus on a different aspect, namely that information is seen as a way to achieve the goal of adopting preventive health behaviors. Through counseling, participants would ultimately benefit from disclosure of the results. Therefore, the PRE-ADS

[63] is the first scale to address the knowledge and support needs of individuals before, during, and after pre-symptomatic screening. Gooblar et al. (2015) [79] only included the need for counseling during the process of pre-symptomatic testing in their scale, and Christensen et al. (2011) [82] have added a question about the individuals' motivation to stay informed about new developments in the treatment and prevention of AD.

One explanation for the fact that the questionnaire results differ between older and younger people, but not between those with a positive or negative family history, is probably that the questionnaire combines too many topics, and it is questionable whether the participants could make an autonomous decision that would include being sufficiently informed. Thus, it would probably be advantageous to ask the questions about benefits and harms first so that the subject can do a cost-benefit analysis. Similarly, questions about possible consequences and lack of information should be asked before questions about acceptability. In addition, there is the question of how much the subjects know about the influence of genetics, how EOAD differs from LOAD, and what conclusions can be drawn from biomarkers or imaging techniques regarding the onset of the first symptoms. This includes education about possible prevention and therapies, which are not yet available for dementia, which is why at least pre-symptomatic genetic testing for AD is considered ethically questionable by professional societies [83]. In the case of genetic testing, there is the additional ethical problem that genetic data are sensitive data, which are also family data [84]. This also explains the finding that there was a significant association between the fear of developing dementia and having a family member with dementia.

Since any medical intervention requires informed consent, in which all questions from the patient must be answered by the physician, a valid questionnaire that captures the acceptability of pre-symptomatic screening would be highly relevant in practice. Braun et al. (2014) [12] used subscale B of the PRISM-PC for this purpose and developed a mini-questionnaire from the original 8 questions, which finally contained 6 questions, 5 of which related to an AD diagnosis, while one question related to a "higher risk of developing AD". The subscale has excellent internal consistency and has been shown in a study of participants in the Berlin Aging Study II (BASE-II) to be acceptable to 72.2% of older adults for routine screening for AD. Following this attempt, we also created a subscale "Acceptability of Screening" consisting of the first 5 items of the PRE-ADS, which belong to the second factor. Consistent with the study by Braun et al. (2014) [12], this scale showed excellent internal consistency. While the focus of the questions in the Braun et al. (2014) [12] scale was on the diagnosis of dementia, the items of the PRE-ADS mainly ask about the risk of developing AD: The first item asks whether someone wants to know their general risk of developing AD, item 3 asks about genetic testing, while items 4 and 5 ask about imaging and biomarkers to diagnose AD (Table 2). As the PRE-ADS is a questionnaire about pre-symptomatic AD and with the knowledge that the pathology of AD can be detected with biomarkers 30 years before the onset of symptoms [85], it would be desirable to adapt the items and to make the difference between pre-symptomatic testing and screening for diagnosis more precise. Item 2 (I would like to be tested regularly with a short questionnaire) is a clear question about the desire to be diagnosed with AD.

Although several studies have examined the acceptability, perceived harms, and perceived benefits of dementia screening [8, 11, 12, 80, 86–88], there remains a dearth of research on attitudes toward pre-symptomatic screening. As the demand for pre-symptomatic screening continues to grow worldwide, the PRE-ADS-D questionnaire could play an important role in future research and help clinicians, policymakers, and other health professionals to better understand the needs and attitudes of the German general population regarding pre-symptomatic testing and AD screening [63]. EFA structured these "attitudes" in terms of their "Concerns about Screening" (factor 1), their "Intention to be Screened" (factor 2), and the chance to benefit from pre-symptomatic testing by adapting "Preventive Health Behaviors" (factor 3). The correlations between the factors were low and insignificant, except for the relatively strong positive correlation between factor 2 "Intention to be Screened" and factor 3 "Preventive Health Behaviors" ($\tau(254) = 0.331$, $p < 0.001$). This relationship is underscored by many similar studies, as many of the described benefits are the most compelling reasons for seeking pre-symptomatic screening [44, 78, 89].

However, it is very essential to interpret the results of this validation study with caution, considering that only the autosomal dominant EOAD, which accounts for 1–5% of all AD cases, is predictive of approximately 80% of EOAD cases [29, 90]. Early detection of this predisposition can be useful for an individual to prepare for the disease in terms of professional and

personal life planning, always respecting the need for genetic counseling and the national legal and ethical frameworks for the predictive diagnosis of genetic diseases [91, 92]. Unlike EOAD, LOAD is determined by a complex interplay between genetic factors (polygenic risk from multiple susceptibility genes), environmental, and lifestyle factors [93, 94]. While *APOE* ε4 is the strongest genetic risk factor for AD, its effect accounts for only 27.3% of the estimated heritability [95]. According to Livingston and colleagues [94, 96], modifiable factors such as hearing loss, physical inactivity, hypertension, and obesity play a significant role in LOAD and have a greater impact than genetics.

The benefits of pre-symptomatic genetic screening should clearly outweigh any potential harms or risks associated with the testing process or the test results in order for it to be considered legitimate [25]. One could argue that early detection of one's genetic predisposition to developing AD through pre-symptomatic screening could lead to preventive behavior that limits the risk of dementia, as discussed in the recommended strategies by Livingston and colleagues [94, 96], a behavior change that is consistent with our third factor, "Preventive Health Behaviors", and that was also observed in the REVEAL Study [44]. However, preventive strategies, such as engaging in regular physical activity, are health recommendations that should generally be followed as they promote overall well-being and reduce the risk of various health conditions, including cardiovascular disease [97, 98], and are not specifically targeted at preventing dementia. In addition, testing for susceptibility genes associated with LOAD can only place individuals in a "risk" category but not resolve their uncertainty [29, 35, 90]. The fact that individuals with positive biomarker screening may not develop AD, while those without a genetic predisposition may still develop AD, underscores the complexity and variability in the relationship between biomarkers, genetic factors, and the development of LOAD [24, 94]. A positive biomarker test can be emotionally distressing for the individual and their family, causing unnecessary anxiety, fear, depression, and stigma [53].

Nevertheless, it is critical to emphasize that biomarker screening for AD has undeniable value for research purposes. A larger database increases the potential to identify additional genes that may play a significant role in predisposing to AD and provide more accurate prognostic information [99]. However, given the current predictive value, the risk of psychological impact, ethical implications and the lack of treatment options, it is not currently advisable to undergo predictive testing for LOAD [21, 22, 100]. The American Geriatrics Society's (AGS) Ethics Committee, therefore, currently recommends genetic testing for LOAD only for diagnostic purposes [83]. Similarly, The German Association for Psychiatry, Psychotherapy, Psychosomatics, and Neurology (DGPPN) and the German Society of Neurology (DGN) advise against predictive testing for the APOE4 allele and suggest that predictive genetic testing accompanied by genetic counseling should be limited to family members of individuals with monogenic forms of dementia [91].

In summary, there are many ethical implications associated with pre-symptomatic genetic screening for AD. As the demand for predictive testing increases, and such tests are more and more accessible to a broader spectrum of society [101], it is necessary to develop informative and consulting programs in order to minimize possible harms. A critical step is to explore society's needs and attitudes toward pre-symptomatic AD screening [63, 80]. Therefore, the PRE-ADS-D questionnaire could be an important tool to explore significant differences in individuals with different socio-demographic characteristics regarding their acceptability, perceived harms, and benefits of pre-symptomatic dementia screening and contribute to the results of other similar studies [9, 78, 80, 87, 102]. These findings can also help to design and tailor health counseling services to meet the individual needs of counselors while respecting cross-cultural differences [58, 63, 80].

Conclusion

The Pre-ADS-D is a reliable and valid tool for assessing attitudes, motivations, and barriers to pre-symptomatic dementia screening in the German general population. One of the main goals of modern science and policy is to empower patients and their families to take an active role. The right to self-determination and autonomy can only be recognized if we have a balanced picture of the wishes of the population, including individuals, patients, and caregivers. Further studies are needed to examine knowledge and attitudes about dementia, but also knowledge about biomarker prediction and genetics, to assess whether participants fully understand the benefits and limitations of these screenings. Otherwise, we cannot be sure that people will not overestimate the prognostic factor and associate

either too much hope with a negative test result or too much stress with a positive one, which is only a risk assessment and far from predicting whether someone will develop dementia. In addition, studies are needed to assess the ethical implications of offering pre-symptomatic dementia screening. As long as the diagnostic and prognostic value is limited, the personal benefit is questionable, especially in the absence of effective therapeutic options.

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CONFLICT OF INTEREST

B.T. is an Editorial Board Member of this journal but was not involved in the peer-review process nor had access to any information regarding its peer-review. I.A.A., H.S., and K.B. have no conflict of interest to report. The European Commission's support for the production of this publication does not constitute an endorsement of the contents, which reflect the views only of the authors, and the Commission cannot be held responsible for any use which may be made of the information contained therein.

DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-230961.

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