Vascular burden and genetic risk in association with cognitive performance and dementia in a population-based study

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ARTICLE INFO
Keywords:
- Cardiovascular prevention
- Vascular risk factors
- Dementia
- Cognitive decline
- Population-based studies

ABSTRACT

Background and purpose: Vascular risk factors may influence cognitive function and thus represent possible targets for preventive approaches against dementia. Yet it remains unknown, if they associate with cognition independently of the individual genetic risk for dementia.

Methods: In a population-based study of 1172 community-dwelling individuals aged ≥65 years in Greece, we constructed a vascular burden score (VBS; based on presence of hypertension, diabetes, hyperlipidemia, heart disease, and cerebrovascular disease, range 0–5) and a polygenic risk score (PRS) for clinically-diagnosed Alzheimer’s disease (AD) based on 23 genetic variants. We then explored in joint models the associations of the PRS for AD and VBS with global cognitive performance, cognitive performance across multiple cognitive domains, and odds of dementia.

Results: The mean age of study participants was 73.9 ± 5.2 years (57.1% females). Both the PRS for AD and VBS were associated with worse global cognitive performance (beta per-SD-increment in PRS: -0.06, 95%CI: -0.10 to -0.02, beta per-point-increment in VBS: -0.05, 95%CI: -0.10 to -0.02), worse performance across individual cognitive domains (memory, executive function, attention, language, visuospatial ability), and higher odds of dementia (OR per-SD increment in PRS: 1.56, 95%CI: 1.05–2.09, OR per-point increment in VBS: 1.38, 95%CI: 1.05–1.81). There was no evidence of an interaction between the two scores. Higher VBS was associated with worse cognitive performance equally across tertiles of the PRS for AD, even among individuals at the highest tertile.

Conclusions: Both genetic risk and vascular burden are independently and additively associated with worse cognitive performance and higher odds of dementia.
Introduction

Dementia is a devastating clinical diagnosis posing a substantial burden on patients, their proxies, and public healthcare systems [1,2]. Given the lack of available treatments for deceleration or regression of cognitive decline, developing effective preventive strategies against cognitive impairment is crucial. Towards this goal, it is important to elucidate the etiology of cognitive impairment in later life. A number of population-based studies have provided evidence about how vascular risk factors associate with the risk of cognitive impairment and dementia in later life [3–7]. Individuals with a higher burden of vascular risk factors and vascular disease show a rapid cognitive decline, faster progression to dementia, and accelerated brain atrophy [8–10]. As vascular risk factors and vascular diseases are potentially modifiable, they have received great attention as potential approaches for prevention of cognitive decline in later life [11].

Yet, moving towards personalized preventive approaches would require considering the individual background risk for dementia. Recent large-scale meta-analyses of genome-wide association studies (GWAS) have provided important insights with regards to genetic factors increasing the risk of Alzheimer’s disease, which underlies 70% of all dementia cases [12,13]. Up to 29 genomic loci have been to date identified as increasing the risk of Alzheimer’s disease [12]. Combining genetic variants in these loci into a polygenic risk score (PRS) could provide important insights about the individual genetic risk for dementia [14]. Indeed, such PRSs predict cognitive decline, the risk of developing mild cognitive impairment and dementia among cognitively normal individuals, as well as the risk of conversion to dementia among individuals with mild cognitive impairment [15,16]. It still remains unclear though whether there is any interaction between the background genetic risk for dementia and the vascular burden score, and thus whether preventive strategies targeting vascular risk factors could offset cognitive decline even among individuals at high genetic risk for dementia.

Here, to address this issue, we use data from a population-based study of 1431 community-dwelling individuals in Greece to explore (i) whether a PRS for Alzheimer’s disease is associated with cognitive performance and odds of dementia, (ii) whether a score representing the burden of vascular risk factors and vascular diseases (vascular burden score, VBS) is associated with cognitive performance and odds of dementia, (iii) whether vascular burden and genetic risk for dementia are jointly associated with cognitive performance and odds of dementia, and (iv) whether vascular burden associates with cognitive performance even among individuals with a high genetic risk for Alzheimer’s disease.

Methods

Study population

Participants for the current study were drawn from the Hellenic Longitudinal Investigation of Aging and Diet (HELIAD) cohort. HELIAD is a population-based, multidisciplinary, collaborative study in Greece. Details about the study design and methodology are detailed elsewhere [17–21]. Briefly, recruitment for the study has been carried out in two different centers, one located in Maroussi, a suburb of Athens and one in the city of Larissa, in central Greece, between 2011 and 2014. Participants were selected through random sampling of community-dwelling individuals of 65 years of age or older. The study has been approved by the Ethics Review Boards of the National and Kapodistrian University of Athens and University of Thessaly. All participants have given written informed consent prior to their participation.

Data collection

In structured standardized face-to-face intensive interviews, study participants provided information regarding their medical history including previous or current diseases, neurological conditions, neuropsychiatric symptoms, current medications, hospitalizations, surgeries and injuries. Medical records of previous diagnoses, physician visits, or hospitalizations were inspected for all participants. Additionally, an extensive structured and standardized physical examination was conducted, evaluating neurological signs and symptoms. Structured questionnaires were used in order to gather information about participants’ functioning, social, mental and physical activities, as well as sleep and dietary habits. Sociodemographic information and information about tobacco use was also collected. Height and weight were measured and body mass index (BMI) was calculated.

Neuropsychological evaluation

The evaluation of cognitive function was performed by neuropsychologists through a comprehensive neuropsychological assessment of all major cognitive domains: (i) orientation (MMSE [22]), non-verbal and verbal memory (medical college of Georgia complex figure test [MCG] [23]; Greek verbal learning test [24]); (ii) language (semantic and phonological verbal fluency [25]; subtests of the Greek version of the Boston naming test-short form, namely, the Boston naming test-short form, and selected items from the complex ideational material subtest, to assess verbal comprehension and repetition of words and phrases [26]); (iii) visuospatial ability (Judgment of Line Orientation [27,28] abbreviated form; MCG complex figure test copy condition [29]; clock drawing test [30]); (iv) attention and information processing speed (trail making test (TMT) Part A [31]); (v) executive functioning (TMT-Part B; verbal fluency; anomalous sentence repetition; graphical sequence test; motor programming [29]; months forwards and backwards), and (vi) a gross estimate of intellectual level (a Greek multiple choice vocabulary test [32]).

Participants’ raw scores on each cognitive test were converted into z-scores using mean and SD values derived from the subset of cognitively normal study participants (no mild cognitive impairment or dementia). Subsequently, these individual neuropsychological test scores were used to produce an average domain composite z-score for memory, executive function, attention, language, and visuospatial ability [33]. The domain-specific composite z-scores were then averaged in order to calculate a global neuropsychological z-score [17]. A higher score indicates better performance. Global cognitive performance was our primary outcome, whereas domain-specific performance was a secondary outcome.

Presence of dementia was also a secondary outcome. Diagnoses of dementia were made according to the DSM-IV-TR criteria [34] in diagnostic consensus meetings including all the researchers and main investigators involved in the project, both neurologists and neuropsychologists. Changes in performance of daily activities and self-care habits that require physical capacity and cognitive functioning, in particular memory, comprehension, calculations and visuospatial orientation, were measured using the Blessed Dementia Scale [35]. The participants’ ability to use the telephone and transportation, medication management and handling of finances independently was assessed using the Lawton Instrumental Activities of Daily Living scale (IADL) [36]. More details regarding the diagnostic procedures followed can be found in previously published work [19,37].

Vascular burden score

A score reflecting the burden of vascular risk factors and vascular disease (VBS) was constructed in accordance with previous studies [9,38]. The presence and number of vascular risk factors for each participant was based on a thorough review of the participant’s medical history, medical records, and medication plan. The VBS for each participant was calculated as the sum of five vascular risk factors and vascular diseases including (i) hypertension (personal history, medical records, receipt of antihypertensive medications), (ii) diabetes mellitus (personal
admission to hospital or any kind of rehabilitation treatment was eligible regarding the date of onset, duration, constellation of symptoms, with stroke or transient ischemic attack. When there was a history of were also interviewed for a history of neurological symptoms consistent with stroke or transient ischemic attack. For stroke and transient ischemic attacks, beyond the standard interview, participants were also interviewed for a history of neurological symptoms consistent with stroke or transient ischemic attack. When there was a history of symptoms suggestive of cerebral ischemia, further information regarding the date of onset, duration, constellation of symptoms, admission to hospital or any kind of rehabilitation treatment was elicited [39]. Presence of each of these risk factors or disease was rated with 1. As such, the final score ranged from 0 to 5.

Genotyping in HELIAD

Genome-wide genotyping was performed at the facilities of the “Centre national de recherche en génétique humaine” (Evry, France) using the Illumina Infinium Global Screening Array (GSA, GSAsharedCUSTOM, 24 + v1.0), as detailed elsewhere [40]. Briefly, variants included in the marker list for removal by Illumina were excluded and only variants for which the full-length probes aligned uniquely on the GRCh38 genome without any mismatch were kept. Variant intensity quality control (QC), was conducted for all autosomal variants, according to established methods [41]. Sample quality control was performed using PLINK v1.9 [42]. Samples with missingness > 0.05, sex inconsistencies or with heterozygosity rate that deviated more than ±5 SD from the mean, were excluded. To identify population outliers, a Principal Component Analysis (PCA), was run using as reference the 1000 Genomes phase 3 population and the dataset was projected onto two dimensions, using the flashPCA2 software [43]. To control for cryptic relatedness, we kept one individual from each pair of samples with a kinship coefficient more than 0.125 (cut-off for second-degree relatives), yielding a final sample size of 1251 unrelated individuals. We excluded variants with a missingness > 0.05 in at least one genotyping center or with a differential missingness test \( p < 10^{-10} \). The Hardy-Weinberg equilibrium tests (\( p < 5 \times 10^{-8} \)) were performed only in controls and for each genotyping center/country separately.

To improve the accuracy of imputation, we compared the frequencies of variants (chi-square test) against two reference panels, the population of the Haplotype Reference Consortium r1.1 (HRC) [44] excluding 1000 Genomes samples and the Finnish and non-Finnish population of Genome Aggregation Database v3 (gnomAD) [45]. Variants showing a \( \chi^2 > 3000 \) in both the HRC and the gnomAD or a \( \chi^2 > 3000 \) in one reference panel without being present in the other were excluded. Finally, GWAS analyses were performed between controls across genotyping centers to assess frequency differences between genotyping centers, using the software SNPTEST [46], under an additive model and adjusting on associated PCs. Variants with a Likelihood Ratio Test of \( p < 10^{-5} \) were excluded. Furthermore, we removed ambiguous variants with minor allele frequency (MAF) > 0.4 and we kept only one copy of any duplicated variants, prioritizing the one with the lowest missingness. All samples and variants, passing the above QC metrics were imputed in the Michigan Imputation Server (v1.2.4) [47] using the TOPMed Freeze 5 reference panel. Phasing and imputation were performed using EAGLE v2.4 [48] and Minimac4 v4.1.0.2 software, respectively.

Construction of genetic risk score for Alzheimer’s disease

Imputed dosages for a total of 5611,082 SNPs with MAF>0.05, call rate >95% and imputation quality score >0.4 were converted to best-guess genotypes for PRS computation. The PRSice software (http://prs ice.info/) was utilized to construct PRSs for each individual applying the clumping and thresholding (C+T) method [49]. A PRS for Alzheimer’s disease was computed, as the weighted sum of the risk increasing alleles that each individual carries at each SNP locus multiplied by the effect size for the reference allele on the basis of large GWAS meta-analysis summary data (i.e. discovery samples) [12]. A set of 23 out of 29 SNPs, which reached genome-wide significance in the original GWAS meta-analysis and were available in our dataset, were used to construct the PRS for Alzheimer’s disease (Supplementary Table 1) [12].

Statistical analysis

First, we explored whether participant characteristics differed between individuals across tertiles of the PRS for Alzheimer’s disease using two-way ANOVA, the Kruskal-Wallis test, or chi-square, as appropriately. To explore the associations of VBS and dementia PRS with cognitive performance, we designed linear regression models including age, sex, years of education, the participants’ VBS and PRS for Alzheimer’s disease, as well as the first two principal components of ancestry. To explore whether the VBS and the PRS for Alzheimer’s disease exert independent effects, we included both of them in the same models. Beyond global cognitive performance, which was our primary outcome, we also explored associations with cognitive performance across the 5 main cognitive domains (memory, executive function, attention, language, visuospatial ability). We also explored the same associations with odds of dementia in logistic regression models including the same variables.

We then explored interactions between the VBS and the PRS for Alzheimer’s disease. For the continuous outcome of cognitive performance, we included the product of the two variables in a linear model and used its coefficient as a measure of additive interaction. For the binary outcome of dementia, we included the interaction term of the two variables in a logistic regression model and used its coefficient as a measure of multiplicative interaction. To assess the interaction on the additive scale, we calculated the relative excess risk due to interaction (RERI); confidence intervals for RERI were calculated using the delta method. We also split the sample in three tertiles depending on participants’ PRS for Alzheimer’s disease and explored associations between of the VBS with global and domain-specific cognitive performance across the tertiles., All analyses were performed using R (v3.6.3; The R Foundation for Statistical Computing).

Results

A total of 1172 individuals with available genetic and cognitive data were included in this analysis (73.9 ± 5.2 years of age, 57.1% females, 6.8 ± 4.5 years of education). The study participants across the three tertiles of a PRS for Alzheimer’s disease did not differ with regards to demographic characteristics or individual vascular risk factors (Table 1). There was evidence of a modest association between the composite VBS and the PRS for Alzheimer’s disease (Supplementary Fig. 1). There were considerable differences with regards to cognitive performance across the three tertiles of PRS for Alzheimer’s disease with individuals with a higher PRS performing lower across cognitive domains (Table 1).

Individuals with a higher vascular burden, as indicated by higher scores in the VBS, also scored worse on cognitive performance and were more likely to be diagnosed with dementia (Fig. 1). In multivariable analyses, both the PRS for Alzheimer’s disease (beta per 1-SD increment: \( \beta = 1.06, 95\%\text{CI}: -0.10 \text{ to } -0.02 \), as well as the VBS (beta per 1-point increment: \( \beta = -0.05, 95\%\text{CI}: -0.09 \text{ to } -0.02 \)) were independently associated with worse global cognitive performance (Table 2). Similar associations were observed across all cognitive domains. Furthermore, both the PRS for Alzheimer’s disease (OR per 1-SD increment: 1.56, 95% CI: 1.17–2.09) and the VBS (OR per 1-point increment: 1.38, 95%CI: 1.05–1.81) were associated with higher odds of dementia (Table 2). For all of these associations, there was no evidence of significant
interactions between the PRS for Alzheimer’s disease and the VBS (Table 2). There was also no evidence of significant deviation from the additive scale in the associations with the odds of dementia (RERI: 0.15, 95%CI: –0.25 to 0.55; Table 2).

Participants scoring higher in VBS showed worse global cognitive performance consistently across the three tertiles of the PRS for Alzheimer’s disease (Fig. 2A). Indeed, in multivariable analyses, VBS showed consistent associations with worse global cognitive performance across all tertiles of the PRS for Alzheimer’s disease (Fig. 2B). Again, similar associations were observed across all cognitive domains.

**Table 1**
Baseline study characteristics by tertiles of the polygenic risk score for Alzheimer’s disease.

| Variable                          | 1st tertile (n = 390) | 2nd tertile (n = 390) | 3rd tertile (n = 392) | p-value |
|-----------------------------------|----------------------|----------------------|----------------------|---------|
| Age, y, mean (SD)                 | 73.6 (5.1)           | 74.2 (5.3)           | 73.9 (5.3)           | 0.355   |
| Female, N (%)                     | 222 (56.9)           | 224 (57.4)           | 223 (56.9)           | 0.985   |
| Education, y, mean (SD)           | 6.9 (4.5)            | 6.8 (4.3)            | 6.9 (4.7)            | 0.967   |
| Hypertension, N (%)               | 265 (69.2)           | 260 (67.7)           | 269 (69.9)           | 0.803   |
| Diabetes mellitus, N (%)          | 62 (16.3)            | 66 (17.2)            | 84 (21.8)            | 0.104   |
| Dyslipidemia, N (%)               | 158 (41.2)           | 156 (40.6)           | 176 (45.7)           | 0.298   |
| Cerebrovascular disease, N (%)    | 27 (7.0)             | 40 (10.4)            | 43 (11.1)            | 0.119   |
| Myocardial infarction, N (%)      | 15 (3.9)             | 14 (3.6)             | 14 (3.7)             | 0.971   |
| BMI, kg/m², mean (SD)             | 29.3 (5.1)           | 29.3 (5.3)           | 29.1 (5.3)           | 0.771   |
| Smoking status                    | 95%CI: –0.25 to 0.55 |
| Current smokers, N (%)            | 40 (10.2)            | 41 (11.2)            | 42 (11.2)            | 0.015   |
| Former smoker, N (%)              | 99 (25.4)            | 113 (29.0)           | 94 (24.0)            | 0.280   |
| Never smokers, N (%)              | 251 (64.4)           | 247 (63.3)           | 254 (64.8)           | 0.043   |
| Vascular burden score, median [Q1-Q3] | 1 [1–2]          | 2 [1–2]              | 2 [1–2]              | 0.048   |
| Global cognitive score, mean (SD) | –0.28 (0.81)        | –0.41 (0.89)         | –0.44 (0.90)         | 0.003   |
| Memory, mean (SD)                 | –0.24 (0.88)         | –0.42 (0.90)         | –0.37 (0.90)         | 0.015   |
| Executive function, mean (SD)     | –0.27 (0.80)         | –0.41 (0.89)         | –0.39 (0.88)         | 0.043   |
| Attention, mean (SD)              | –0.33 (1.18)         | –0.43 (1.23)         | –0.47 (1.29)         | 0.313   |
| Language, mean (SD)               | –0.29 (0.90)         | –0.40 (0.97)         | –0.36 (0.95)         | 0.297   |
| Visuospatial ability, mean (SD)   | –0.19 (0.50)         | –0.36 (0.97)         | –0.28 (0.95)         | 0.152   |
| Dementia, N (%)                   | 11 (2.8)             | 16 (4.1)             | 20 (5.1)             | 0.171   |

**Table 2**
Associations between the polygenic risk score for Alzheimer’s disease and vascular burden score with cognitive outcomes from joint models including both variables.

| Outcome                        | Exposure*                    | Association estimate beta (95%CI) | p-value |
|--------------------------------|------------------------------|----------------------------------|---------|
| Cognitive performance          |                              |                                  |         |
| Global cognitive function      | PRS                          | –0.06 (–0.10 to 0.02)            | 0.002   |
|                               | VBS                          | –0.05 (–0.09 to 0.02)            | 0.003   |
|                               | Interaction                  | 0.359                            |         |
|                               | Memory PRS                   | –0.07 (–0.12 to 0.03)            | 0.861   |
|                               | VBS                          | –0.02 (–0.05 to 0.02)            | 0.002   |
|                               | Interaction                  | 0.370                            |         |
|                               | Executive function PRS       | –0.04 (–0.08 to 0.00)            | 0.048   |
|                               | VBS                          | –0.04 (–0.08 to 0.03)            | 0.001   |
|                               | Interaction                  | 0.972                            |         |
|                               | Attention PRS                | –0.10 (–0.16 to 0.03)            | 0.003   |
|                               | VBS                          | –0.09 (–0.15 to 0.03)            | 0.003   |
|                               | Interaction                  | 0.927                            |         |
|                               | Language PRS                 | –0.04 (–0.08 to 0.01)            | 0.077   |
|                               | VBS                          | –0.05 (–0.08 to 0.01)            | 0.016   |
|                               | Interaction                  | 0.851                            |         |
|                               | Visuospatial ability PRS     | –0.04 (–0.10 to 0.02)            | 0.194   |
|                               | VBS                          | –0.06 (–0.12 to 0.01)            | 0.019   |
|                               | Interaction                  | 0.359                            |         |
| Odds of dementia               |                              |                                  |         |
| Dementia PRS                   | OR (95%CI)                   | 1.56 (1.17–2.09)                | 0.003   |
|                                | VBS                          | 1.38 (1.05–1.81)                | 0.018   |
|                                | Additive interaction*        |                                  | 0.460   |
| Multinominal interaction*      |                              |                                  | 0.563   |

* The polygenic risk score (PRS) for Alzheimer’s disease is analyzed in increments of 1 standard deviation, whereas vascular burden score (VBS) is analyzed in 1-point increments (range 0–5).

**Fig. 1.** Global cognitive performance and prevalence of dementia across the range of the vascular burden score.

**Discussion**

In this population-based study of 1172 community-dwelling individuals in Greece, both a higher VBS and a higher PRS for Alzheimer’s disease were additively and independently of each other associated with worse global cognitive performance, worse domain-specific cognitive performance and higher odds of dementia. Across tertiles of the PRS for Alzheimer’s disease, a higher VBS was equally associated with worse global cognitive performance. Even among individuals at highest genetic risk for dementia, VBS was still significantly associated with worse cognitive performance.

These data provide additional support to the notion of focusing on the modification of vascular risk factors and prevention of vascular disease in order to decrease the rates of dementia [30,51]. While several previous studies have provided evidence that vascular risk factors associate with the risk of dementia and cognitive impairment, it remained unclear if this risk is independent of the individual (Supplementary Fig. 2).
background genetic risk for dementia. Here, we show that there is no evidence of interaction between vascular burden and genetic dementia risk when it comes to their associations with cognitive performance and dementia. Furthermore, we show that even among individuals with a high baseline genetic risk for dementia, their vascular burden is still independently associated with cognitive performance. These results could serve as a basis for future post hoc analyses of clinical trials testing whether vascular risk factor modification, such as blood pressure lowering \[52\], could offset risk for cognitive decline even among individual at high genetic risk for dementia.

Our findings confirm and extend previous studies showing that modifiable risk factors can contribute to the risk of dementia independently of the individual genetic risk score for dementia. A study of 196,383 individuals in the population-based UK Biobank showed that a healthy lifestyle profile, as indicated by no current smoking, regular physical activity, healthy diet, and moderate alcohol consumption, was associated with a lower risk of dementia even among individuals at the highest genetic risk quantile for dementia \[53\]. Furthermore, among 1211 individuals of the Framingham Heart Study, low cardiovascular health index \[54\], was associated with a lower risk of incident dementia independently of a genetic risk score for dementia \[55\]. In the current study, we expand these findings beyond the hard outcome of dementia to performance across the entire spectrum of cognitive function. Furthermore, we use a burden index that beyond vascular risk factors, also incorporates information on presence of vascular disease including history of heart disease and cerebrovascular disease.

Several strengths of the current study should be noted. First, this is a population-based study representative of the general elderly population of community-dwelling individuals. Second, the extensive cognitive testing allowed for multiple layers of analyses with regards to cognitive performance. Third, a highly structured approach was followed for determining diagnoses of dementia involving a consensus meeting of neurologists and neuropsychologists on the basis of a detailed cognitive and functional assessment and inspection of all medical records of the participants.

This study has several limitations. First, the prevalence of dementia was relatively low in the overall sample (4%), probably reflecting an underrepresentation of individuals at high risk for dementia in the examined population. This may influence the external validity of our findings or add collider bias in the reported associations if the genetic Fig. 2. Associations of the vascular burden score with cognitive performance across tertiles of the polygenic risk score (PRS) for Alzheimer’s disease. (A) Global cognitive performance across tertiles of the PRS for Alzheimer’s disease by vascular burden score. (B) Results from linear regression regarding the effects of vascular burden score (1-point increment) across tertiles of the PRS for Alzheimer’s disease. Results for panel B are derived from multivariable models including age, sex, years of education, vascular burden score (VBS), and the first two ancestry principal components.
score or the vascular risk factors also influenced participation in the study. Second, our analyses represent cross-sectional associations and cannot be used to establish causal associations between vascular burden and cognition, as reverse causation cannot be excluded. Third, unlike the genetic risk score for dementia, individuals were not randomly assigned to the vascular burden score and its associations with cognition could be biased by confounding. Fourth, this study is restricted to individuals of European ancestry and the results may thus not be generalizable to other populations. Fifth, several of our analyses have been limited by a relatively small sample size leading to uncertainty in many of the estimates, especially those referring to odds of dementia. Sixth, despite a rigorous evaluation of all individuals by neurologists and examination of pharmacotherapy and other background medical records (if available by participants), information for the vascular burden score was to a large extent based on self-report.

Conclusions

In conclusion, in a community-based sample, vascular risk and genetic risk associate with cognitive performance, and odds of dementia additively and independently of each other. Even among individuals at high genetic risk for dementia, a low vascular burden is associated with better cognitive performance. Whether targeting vascular risk factors could offset a high genetic risk score for dementia should be further explored in future studies.

Sources of funding

This work has been supported by the following grants: IRRG-09-133,014 from the Alzheimer’s Association, 189 10,276/8/9/2011 from the NSRF-EU program Excellence Grant (ARISTEIA), which is co-funded by the European Social Fund and Greek National resources, and ΔΥ/οικ.51657/14.4.2009 from the Ministry for Health and Social Solidarity (Greece). MG acknowledges support in form of a Walter-Solidarity (Greece). MG acknowledges support in form of a Walter-Solidarity (Greece).

Declaration of Competing Interest

Nothing to report.

Acknowledgements

We would like to thank the participants of the study and their families for agreeing to participate in the study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cccb.2022.100145.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cccb.2022.100145.
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