NeuroImage 232 (2021) 117899

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

CSF dynamics as a predictor of cognitive progression

Petrice M. Cogswell[a,*], Stephen D. Weigand[b], Heather J. Wiste[b], Jeffrey L. Gunter[a,c], Jonathan Graff-Radford[d], David T. Jones[d], Christopher G. Schwarz[a], Matthew L. Senjem[a,c], David S. Knopman[d], Ronald C. Petersen[b,d], Clifford R. Jack Jr[a]

[a] Department of Radiology, Mayo Clinic, 200 First St SW, Rochester, MN 55905, USA
[b] Department of Health Sciences Research, Mayo Clinic, 200 First St SW, Rochester, MN 55905, USA
[c] Department of Information Technology, Mayo Clinic, 200 First St SW, Rochester, MN 55905, USA
[d] Department of Neurology, Mayo Clinic, 200 First St SW, Rochester, MN 55905, USA

ARTICLE INFO

Keywords:
Disproportionately enlarged subarachnoid-space hydrocephalus
MRI
Cognitive impairment

ABSTRACT

Disproportionately enlarged subarachnoid-space hydrocephalus (DESH), characterized by tight high convexity CSF spaces, ventriculomegaly, and enlarged Sylvian fissures, is thought to be an indirect marker of a CSF dynamics disorder. The clinical significance of DESH with regard to cognitive decline in a community setting is not yet well defined. The goal of this work is to determine if DESH is associated with cognitive decline. Participants in the population-based Mayo Clinic Study of Aging (MCSA) who met the following criteria were included: age ≥ 65 years, 3T MRI, and diagnosis of cognitively unimpaired or mild cognitive impairment at enrollment as well as at least one follow-up visit with cognitive testing. A support vector machine based method to detect the DESH *imaging features* on T1-weighted MRI was used to calculate a "DESH score", with positive scores indicating a more DESH-like imaging pattern. For the participants who were cognitively unimpaired at enrollment, a Cox proportional hazards model was fit with time defined as years from enrollment to first diagnosis of mild cognitive impairment or dementia, or as years to last known cognitively unimpaired diagnosis for those who did not progress. Linear mixed effects models were fit among all participants to estimate annual change in cognitive z scores for each domain (memory, attention, language, and visuospatial) and a global z score. For all models, covariates included age, sex, education, APOE genotype, cortical thickness, white matter hyperintensity volume, and total intracranial volume. The hazard of progression to cognitive impairment was an estimated 12% greater for a DESH score of +1 versus −1 (HR 1.12, 95% CI 0.97–1.31, $p = 0.11$). Global and attention cognition declined 0.015 (95% CI 0.005–0.025) and 0.016 (95% CI 0.005–0.028) z/year more, respectively, for a DESH score of +1 vs −1 ($p = 0.01$ and $p = 0.02$), with similar, though not statistically significant DESH effects in the other cognitive domains. Imaging features of disordered CSF dynamics are an independent predictor of subsequent cognitive decline in the MCSA, among other well-known factors including age, cortical thickness, and APOE status. Therefore, since DESH contributes to cognitive decline and is present in the general population, identifying individuals with DESH features may be important clinically as well as for selection in clinical trials.

1. Introduction

Disproportionately enlarged subarachnoid-space hydrocephalus (DESH), characterized by tight high convexity CSF spaces, ventriculomegaly, and enlarged Sylvian fissures, is thought to be an indirect marker of a CSF dynamics disorder (Hashimoto et al., 2010; Kitagaki et al., 1998). The imaging phenotype was originally described in normal pressure hydrocephalus (NPH), a clinical syndrome characterized by gait dysfunction, cognitive decline, and urinary incontinence (Adams et al., 1965). DESH has been found to predict clinical improvement in NPH symptomatology following CSF shunting (Hashimoto et al., 2010; Narita et al., 2016). DESH has since been more widely recognized in the community and has been found to be associated with worse cognition (Akiba et al., 2020; Graff-Radford et al., 2019; Hiraoka et al., 2008). Although few studies have shown the presence of DESH imaging features in community or non-NPH study populations, the clinical significance of DESH with regard to cognitive decline outside of NPH is not yet well defined.

DESH is most commonly detected on visual review of MR exams via qualitative assessment for ventriculomegaly, tight high convexity or midline sulci, and enlargement of the Sylvian fissures or focally enlarged sulci. Quantitative measures such as the Evan's index and callosal angle may also be used for assessment of ventriculomegaly and tight high

* Corresponding author.
E-mail address: Cogswell.petrice@mayo.edu (P.M. Cogswell).

https://doi.org/10.1016/j.neuroimage.2021.117899
Received 14 January 2021; Accepted 17 February 2021
Available online 23 February 2021

convexity, respectively. More recently, an automated method has been developed to detect DESH neuroimaging features on T1-weighted MRI and to calculate a "DESH score" (Gunter et al., 2019). Application of an automated detection method for DESH imaging features facilitates evaluation of these imaging features in large study populations with a more standardized assessment compared to qualitative reader review. The goal of this work is to apply the computational DESH algorithm to determine if higher DESH scores are associated with worse cognition in a longitudinal cohort study.

2. Materials and methods

2.1. Participants, inclusion criteria

All participants were enrolled in the Mayo Clinic Study of Aging (MCSA), a longitudinal cohort study of residents of Olmsted Co., Minnesota (Roberts et al., 2008). For inclusion in this study, participants were required to have a 3T GE MRI, a diagnosis of cognitively unimpaired or mild cognitive impairment, and be 65 years of age or older at enrollment. A small number of participants (n=20) were excluded due to missing covariates of interest (APOE genotype, white matter hyperintensity [WMH] volume estimate, or FreeSurfer cortical thickness estimate). Participants were also required to have at least one follow-up visit with cognitive assessments. The age range was chosen based on the low prevalence of DESH below the age of 65 years. The study was approved by the Mayo Clinic and Olmsted Medical Center institutional review boards. All participants provided written informed consent; consent was obtained from a legally authorized representative for cognitively impaired participants.

2.2. Cognitive assessment

MCSA visits occur approximately every 15 months. At each study visit a mental status examination, neurologic examination, and neuropsychological examination were performed along with a review of the participant's medical history. The neuropsychological examination included nine tests to evaluate the four cognitive domains of memory (Auditory Verbal Learning Test Delayed Recall, Wechsler Memory Scale-Revised [WMS-R] Logical Memory-II, and Visual Reproduction-II Delayed Recall), attention-executive function (Trail Making Test B and Wechsler Adult Intelligence Scale-Revised [WAIS-R] Digit Symbol), language (Boston Naming Test and Category Fluency), and visuospatial skills (WAIS-R Picture Completion and Block Design). Z scores were calculated for each domain, and the z scores across all domains were averaged and scaled to generate a global z score. Based on clinical evaluations, a consensus panel classified participants as cognitively unimpaired, having mild cognitive impairment (Petersen, 2004), or having dementia (Blacker et al., 1994). Further details have been previously published (Roberts et al., 2008). For inclusion in this study, individuals were required to have a baseline and follow-up z score for one or more domains. The z scores were based on the cognitive performance of cognitively unimpaired MCSA participant's age 50 years and older weighted to the 2013 Olmsted Co. population.

2.3. Composite cardiovascular and metabolic conditions score

The composite cardiovascular and metabolic conditions (CMC) score was calculated for each participant. The CMC score is a sum of seven conditions that are indicators of vascular health: hypertension, hyperlipidemia, cardiac arrhythmia, coronary artery disease, congestive heart failure, diabetes mellitus, and stroke (Rocca et al., 2014).

2.4. Imaging

Imaging was performed on a 3T GE system (GE Healthcare, Waukesha, WI) and included three-dimensional T1-weighted magnetization prepared rapid gradient echo (MPRAGE) and two-dimensional T2-weighted fluid-attenuated inversion recovery (FLAIR) imaging. MPRAGE acquisition parameters were TR/TE 7.4/3.0 ms, TI 900 ms, flip angle 8°, FOV 260 × 260 mm, matrix 256 × 256, phase FOV 94%, slice thickness 1.2 mm. T2-weighted FLAIR acquisition parameters were TR/TE 11000/154.6 ms, TI 2250 ms, flip angle 90°, FOV 220 × 220 mm, matrix 256 × 192, slice thickness 3 mm.

2.5. Calculating DESH scores

A support vector machine-based method to detect DESH imaging features on MPRAGE T1-weighted MRI was used to calculate DESH scores (Gunter et al., 2019). The input to the algorithm was sulcal (CSF space) regions of interest volumes, normalized to total intracranial volume. The algorithm used these sulcal regions of interest to predict an expert reader's classification of DESH, based on MRI features of tightness of sulci at the high convexity and along the midline of the cerebral hemispheres. As ventriculomegaly and enlargement of the Sylvian fissures may also be seen in the setting of aging and neurodegenerative processes, the presence of high convexity tight sulci was weighted more highly in the algorithm. The algorithm outputs a DESH score where positive values indicate the presence of more "DESH-like" features and negative values indicate less "DESH-like" features (Fig. 1).

2.6. Cortical thickness

The MPRAGE images were used to estimate cortical thickness using FreeSurfer 5.3 (Fischl and Dale, 2000). The temporal meta-ROI, a surface area weighted average of the mean thickness in the entorhinal, fusiform, middle temporal, and inferior temporal regions-of-interest was used as a summary measure of cortical thickness (Jack et al., 2017). We also estimated total intracranial volume (TIV) from the MPRAGE images using the Mayo Clinic Adult Lifespan Template (MCALT) pipeline (https://www.nitrc.org/projects/mcalt/) (Schwarz et al., 2017).

2.7. White matter hyperintensity volume

The 3D MPRAGE and 2D T2-weighted FLAIR images were used to calculate white matter hyperintensity (WMH) volume via a fully-automated algorithm, updated from a previously described in-house semi-automated method (Raz et al., 2013). Total WMH volume was calculated as cm^3.

2.8. Statistical analysis

Two different types of models were used to evaluate the DESH score as a predictor of cognitive decline. A Cox proportional hazards model was fit among only the participants who were cognitively unimpaired at MCSA enrollment and was used to assess progression to a diagnosis of cognitive impairment. Event time was defined as years from study enrollment to the first visit with a diagnosis of mild cognitive impairment or dementia. Participants who did not progress to cognitive impairment were censored at their last visit with a diagnosis of cognitively unimpaired.

Among all participants, linear mixed effects models were used to evaluate the effect of the DESH score on the annual change in continuous measures of cognition: memory, language, attention, visuospatial, and global z scores. A separate model was fit for each domain with the domain z scores as the outcome. Time was defined as years from first MCSA visit. Although we only evaluated longitudinal effects in this work, the linear mixed model was parameterized such that the covariates could affect both the baseline (cross-sectional) z score in addition to the rate of annual change in z score (i.e. time × covariate). All models included participant-specific random intercepts and slopes.

Both the Cox proportional hazards and linear mixed effects models included the following covariates obtained at the enrollment visit: DESH

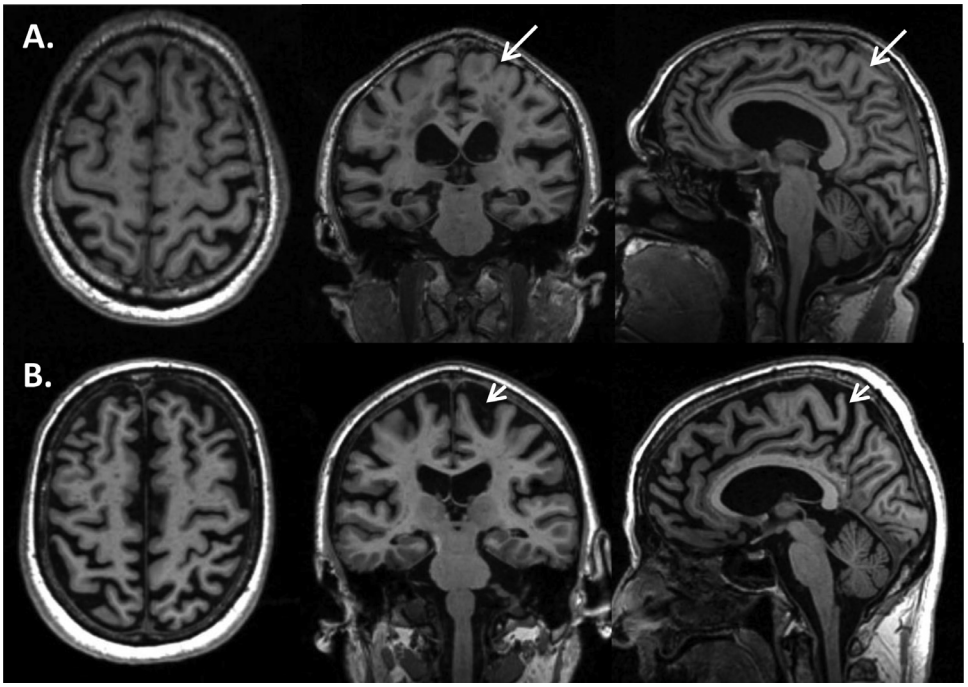

Fig. 1. Examples of participants with positive and negative DESH scores. (A.) Participant identified as having DESH-like MRI features by the automated algorithm with a positive DESH score of 3.2. Relative narrow sulci at the vertex is shown by the arrows. (B.) Participant with a negative DESH score of -3.0, indicating absence of DESH features. Diffuse sulcal widening is indicative of atrophy (arrow heads).

score, age, sex, education, APOE ε4 genotype, CMC score, cortical thickness, TIV, and WMH volume. The DESH score and age were modelled as restricted cubic splines with knots at DESH scores of −1, 0, and 1 and ages 70, 77, and 85 to allow for potential non-linear effects. WMH volume was modelled with a log-transformation. Education was treated as a three-level categorical variable with high school or less, some college, and college graduate as the levels.

Age, sex, education, APOE genotype, and cortical thickness were included as covariates as they are well-established predictors of cognitive decline. WMH volume was included in the model as it has been shown to predict cognitive decline (Au et al., 2006; Fiford et al., 2020; Wang et al., 2020) and to be associated with DESH (Graff-Radford et al., 2019). TIV was included as it may be relevant when considering WMH volume (Au et al., 2006). CMC was included to control for comorbidities in the cohort.

The standard interpretation of coefficients in the Cox model or mixed effects model would be the log relative hazard or the difference in annual rate of change for a 1-unit difference in the predictor. However, a 1-unit difference in the predictor may not be easily interpretable given the scale of the predictors. We therefore report effects for clinically meaningful contrasts. Since the models allowed for non-linearity in age, we summarize three age comparisons: 75 vs. 70, 80 vs. 75, and the 10-year difference of 80 vs. 70. Similarly, we summarize three DESH score comparisons: 1 vs 0, 0 vs. −1, and 1 vs −1. DESH scores of 1 and −1 correspond to positive/abnormal and negative/normal.

We report p-values for each covariate. Age, education, and DESH score p-values are based on 2 degree of freedom tests. All analyses were done using the R language and environment for statistical computing version 3.6.2.

2.9. Secondary analyses

As cortical thickness and WMH volume may themselves be affected by a DESH pattern, we performed a secondary analysis excluding these two covariates.

2.10. Data availability

Numeric data underlying these analyses may be made available to investigators upon reasonable request, via submission of a request to the MCSA executive committee.

3. Results

3.1. Participants

The study included 1208 participants with cognitive follow-up for at least one domain z score. The number of participants with domain z scores at baseline and follow-up varied across the domains with the numbers available for analysis of each domain as follows: 1201 for memory, 1174 for attention, 1178 for language, 1166 for visuospatial, and 1141 for global. Participant characteristics are summarized in Table 1 for the participant group as a whole and for the subset of cognitively unimpaired participants at baseline. In the overall sample, the median age was 76 years (IQR 72–82) and 47% were female. A little over a third of the sample (36%) had a college education and 27% were APOE ε4 carriers. Participants had a median of two cardiovascular and metabolic conditions (IQR 1–3). DESH scores ranged from −14.5 to 6.8 with the median score of −1.7 (IQR −2.9, −0.4). Median follow-up was six years.

3.2. DESH score as a predictor of diagnostic categorical progression

Of the 1050 participants who were cognitively unimpaired at baseline, 278 progressed from cognitively unimpaired to MCI or dementia during the study follow-up period. After adjusting for an extensive set of clinical and imaging covariates, a DESH score of +1 versus −1 was associated with approximately 12% greater hazard of progression (HR 1.12, 95% CI 0.97–1.31), though this effect did not reach statistical significance ($p = 0.11$, **Fig. 2**). While the model allowed for non-linearity in the DESH score association with progression, the hazard ratios for DESH scores of +1 vs 0 and 0 vs −1, were quite similar (HR 1.05 and 1.07, respectively). The DESH score effect was of similar magnitude to those reported for CMC score, log WMH volume, and sex. Older age (80 vs. 75), lower education group (high school or less vs. college grad), APOE ε4 genotype (carrier vs. non-carrier), and a thinner cortex (2.5

Table 1
Characteristics of the sample overall and within the subset of cognitively unimpaired participants.

Characteristic	Overall* (n=1208)	Cognitively unimpaired* (n=1050)
Age, y		
Median (IQR)	76 (72, 82)	75 (72, 81)
Range	65 to 92	65 to 91
Sex, n (%)		
Female	571 (47%)	507 (48%)
Male	637 (53%)	543 (52%)
Education, n (%)		
High school or less	466 (39%)	376 (36%)
Some college	308 (25%)	278 (26%)
College grad	434 (36%)	396 (38%)
APOE ε4, n (%)		
Non-carrier	883 (73%)	771 (73%)
Carrier	325 (27%)	279 (27%)
Cardiovascular and metabolic conditions score		
Median (IQR)	2 (1, 3)	2 (1, 3)
Range	0 to 7	0 to 7
Clinical diagnosis		
Cognitively unimpaired	1050 (87%)	1050 (100%)
Mild cognitive impairment	158 (13%)	0 (0%)
Short Test of Mental Status score		
Median (IQR)	35 (32, 36)	35 (33, 37)
Range	20 to 38	26 to 38
Cortical thickness, mm		
Median (IQR)	2.6 (2.5, 2.7)	2.7 (2.6, 2.7)
Range	2.0 to 3.0	2.1 to 3.0
WMH volume, cm^3		
Median (IQR)	13 (7, 24)	12 (7, 21)
Range	0 to 169	0 to 169
DESH score		
Median (IQR)	-1.7 (-2.9, -0.4)	-1.7 (-2.9, -0.4)
Range	-14.5 to 6.8	-12.3 to 6.8
Follow-up, y		
Median (IQR)	6 (4, 9)	7 (4, 9)
Range	1 to 14	1 to 14

* The overall sample was used for the longitudinal z score models and the subset of cognitively unimpaired individuals was used for the time to event analysis.

vs. 2.7 mm) showed a much larger association with progression, with about a 60% greater hazard of progression to cognitive impairment.

3.3. DESH score as a predictor of decline on continuous measures of specific cognitive domains

In the cohort as a whole, global cognition declined by 0.08 (95% CI 0.07–0.09) z/year. Memory declined by less (estimate −0.03, 95% CI −0.04 to −0.02 z/year) and attention by slightly more (estimate: −0.11, 95% CI −0.12 to −0.10 z/year). Results of linear mixed effects models of the annual change in global, memory, attention, language, and visuospatial domain z scores are shown in Fig. 3. Higher DESH score was significantly associated with a greater annual decline in z score for the attention domain (p = 0.02) and global z score (p = 0.01). Attention declined by 0.016 (95% CI 0.005–0.028) z/year faster and global cognition declined by 0.015 (95% CI 0.005–0.025) z/year faster for a DESH score of 1 compared to −1. There was some non-linearity in the DESH effect with greater cognitive declines for DESH scores of 1 vs 0 (estimate −0.013 z/year for attention and global) but very little difference in decline for DESH scores of 0 vs −1 (estimate −0.003 and −0.002 z/year for attention and global). The DESH score associations were similar in the memory, language, and visuospatial domains (estimates −0.010, −0.012, and −0.010 z/year, respectively, for a DESH score of 1 vs. −1), though not statistically significant.

For the global z score, the effect of the DESH score on annual change was similar to that of a difference in log-transformed WMH volume of 15 vs 5 cm^3 (−0.010) and a difference in 2 vs 0 conditions for the CMC score (−0.008). Older age (80 vs. 75), APOE ε4 genotype (carrier vs. non-carrier), and thinner cortex (2.5 vs. 2.7 mm) showed the greatest effect on annual rate of change on global z score with an approximately 0.04 z/year greater decline. The effect of sex on annual change in global z score was slightly less at 0.03 z/year greater decline for females compared to males. Education had minimal effect on the annual change in global z score. Similar trends among the covariates were present for the individual cognitive domains.

3.4. Models fit without cortical thickness and WMH volume as covariates

In the Cox proportional hazard models fit without cortical thickness and WMH volume, a DESH score of +1 versus −1 was associated with approximately 20% greater hazard of progression to cognitive impairment (HR 1.20, 95% CI 1.04–1.39, p = 0.02), a slightly greater effect size than seen in the full model. The effect sizes of age, sex, CMC, and TIV also slightly increased (Supplemental Fig. 1).

In the linear mixed effects models fit without cortical thickness and WMH, global and attention cognition declined by 0.019 (95% CI 0.009–0.029, p < 0.001) and 0.020 (95% CI 0.009–0.031, p = 0.002) z/year faster for a DESH score of 1 compared to −1, slightly greater effect sizes than seen in the full models. For the other individual cognitive domains, the effect of the DESH score on annual z score change also increased when omitting cortical thickness and WMH volume from the model. With these small changes, the DESH score reached statistical significance in all domains ($p \leq 0.02$). The estimates of difference in annual change in cognitive z score also slightly increased for age, CMC, and TIV (Supplemental Fig. 2).

4. Conclusions

In this study we evaluated an automated DESH score, an indirect marker of a CSF dynamics disorder, as a predictor of cognitive decline

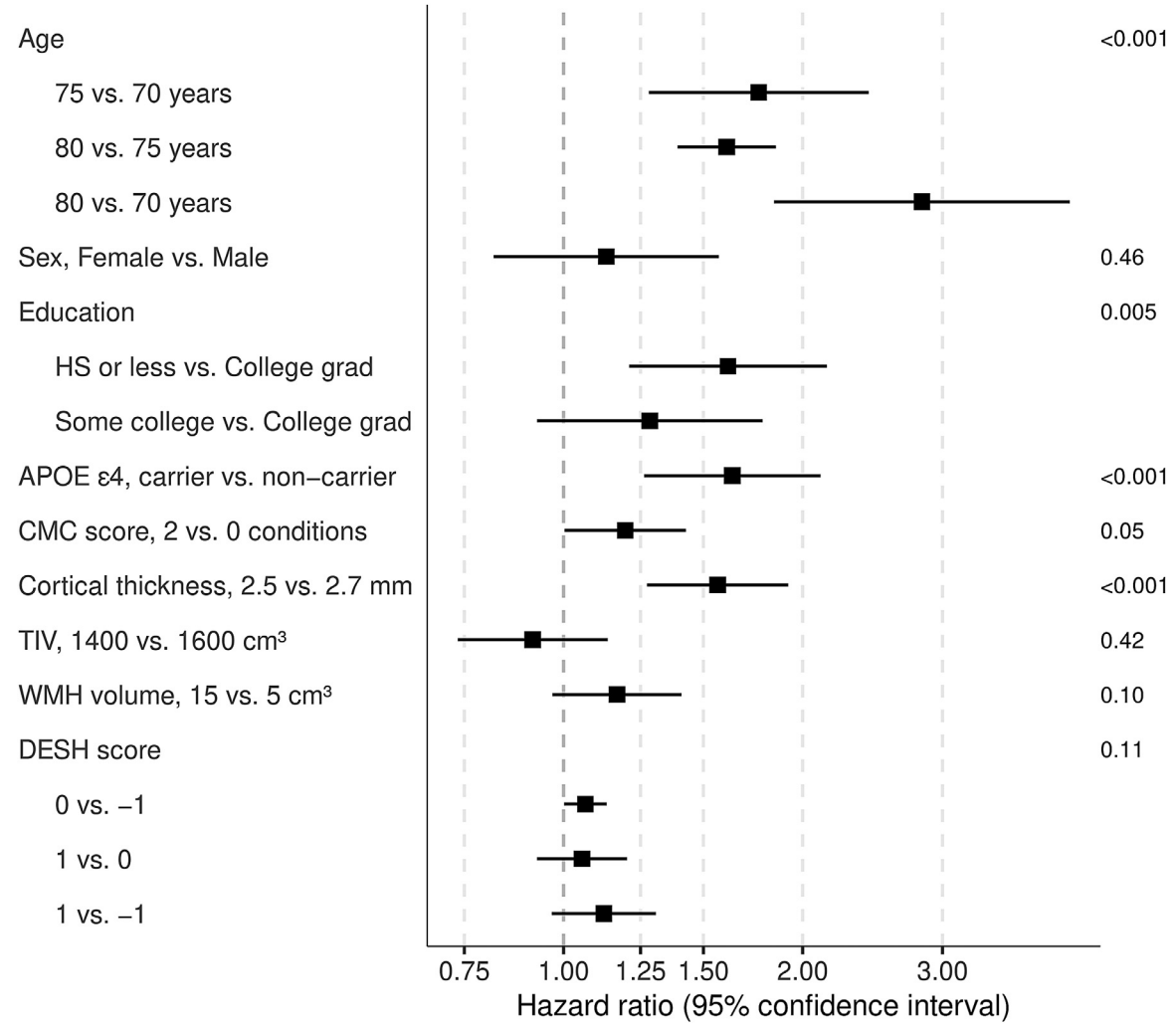

Fig. 2. Hazard ratio estimates with 95% confidence intervals shown on a log scale. Estimates are from a multivariable Cox proportional hazards model predicting progression from cognitively unimpaired to MCI or dementia. The model includes the following variables: age, sex, education (high school [HS] or less, some college, college graduate), APOE genotype, CMC score, cortical thickness, TIV, WMH volume, and DESH score. Age and DESH were modeled as restricted cubic splines with knots at ages 70, 77, 85 and DESH scores of −1, 0, 1. WMH volume was log-transformed. There were a total of 1050 individuals and 278 events used in the model. P-values are shown on the right side of the plot.

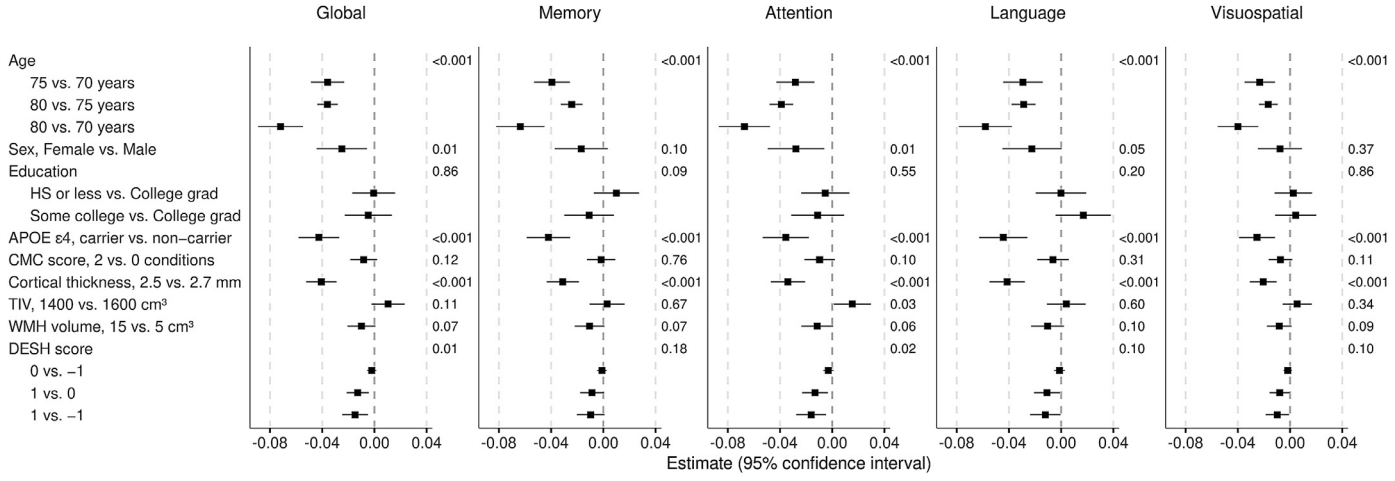

Fig. 3. Estimated mean (95% confidence interval) difference in annual change in cognitive z score for contrasts of interest. Estimates are from multivariable linear mixed effects models fit separately within each domain. The models included the following variables recorded at MCSA enrollment as terms that could affect both the baseline (cross-sectional) z score and the rate of annual change in z score (i.e. time x covariate): age, sex, education (high school [HS] or less, some college, college graduate), APOE genotype, CMC score, cortical thickness, TIV, WMH volume, and DESH score. Age and DESH score were modeled as restricted cubic splines with knots at ages 70, 77, 85 and DESH scores of −1, 0, 1. WMH volume was log-transformed. P-values are shown on the right side of each panel.

in the MCSA. Controlling for established predictors of cognitive decline, including age, sex, comorbidities, cortical thickness, and white matter hyperintensity volume, the DESH score was shown to be an independent predictor of cognitive decline with a modest effect size. CSF dynamics disorders are under appreciated in the medical and research communities as a contributor to cognitive decline, and the specific contribution of CSF dynamics disorders to cognitive decline in the community-based aging population is currently unknown. In an aging community population such as the MCSA, cognitive decline is generally due to multiple etiologies, and our data suggest that disordered CSF dynamics underlying a higher DESH score is one of them.

In the model predicting categorical progression from CU to MCI or dementia, we found evidence that a higher DESH score was associated with a slightly higher rate of progression. In the evaluation of individual cognitive domains, the DESH score was an independent predictor of annual z score change. Although the annual change in z score was statistically significant for only the global and attention domains, a similar effect size was obtained for the other cognitive domains, and the results are largely consistent across domains. The effect of the DESH score on annual change in z score was non-linear, with scores above 0, indicating more DESH-like features, primarily being associated with a greater decline. Scores less than 0, indicating less-DESH like features, had little effect on annual z score change. Non-linearity may be due to low DESH score being non-specific, as non-DESH like features may be seen in participants with a normal brain MR who remain cognitively unimpaired during the study time interval or in participants with atrophy and neurodegeneration-related cognitive decline.

In both the categorical progression and z score analyses, the effect size of the DESH score was similar to those reported for accepted indicators of cerebrovascular disease (WMH volume and CMC score), which is generally regarded as the second most common co-pathology underlying age-related cognitive impairment. As may be expected, established risk factors of older age, APOE ε4 genotype, and thinner cortex had a greater effect on cognitive decline. Because cognitive decline in the aging population is generally due to multiple etiologies, a direction of research is to identify every contributor to cognitive decline. Although the effect size of the DESH score is less than other covariates, it is important for the medical and research communites to be aware of this contributor to cognitive decline. Additionally, by design, MCSA participants have a wide range of pathology and disease stages, which may make detecting effects of disordered CSF dynamics more difficult than in a targeted population thought to have primarily disordered CSF dynamics driving cognitive impairment.

The non-DESH predictor variables in both the Cox proportional hazards and linear mixed effects models showed effects similar to prior studies, with older age, APOE ε4 genotype, thinner cortex, and greater WMH volume associated with cognitive impairment and cognitive decline (Au et al., 2006; Bangen et al., 2018; Tilvis et al., 2004; Wang et al., 2020). As in prior work, a higher level of education showed relatively weak and variable effects on the annual change among domain z scores (Alley et al., 2007; Wilson et al., 2009), while in the model predicting categorical progression to cognitive impairment, the hazard ratio for education (high school or less vs college graduate) was similar to APOE ε4 genotype, cortical thickness, and age 80 vs 75.

The established primary pathologies contributing to cognitive decline (that can be measured in vivo) have been adjusted for in our models to isolate the effect of the DESH score and disordered CSF dynamics. Some of the covariates included in this study may be related to the development of DESH, either as a cause or effect, though these relationships have not yet been well-established. Specifically, CSF dynamics may influence cortical thickness and WMH volume. If so, it may be hypothesized that the DESH score effect we report only reflects direct effects of a DESH pattern on cognition, and not both direct and indirect effects. Therefore, as secondary analyses, models were fit without cortical thickness and WMH volume as covariates. These models showed similar results to the primary analyses with slightly greater effect sizes for the DESH score. The interplay of DESH with cortical thickness and WMH volume is likely complex and not specifically evaluated in this work. The narrowing of the sulci at the vertex in DESH appears to cause mechanical compression of the cortex, and dilated CSF spaces elsewhere could similarly result in apparent lowering of the cortical thickness. WMH volume has been shown to be associated with a clinicoradiologic diagnosis of NPH as well as DESH in community populations. This association may be due to a combination of interstitial edema and chronic small vessel ischemic changes, though the mechanism of interaction and initiating events remain unclear (Bradley et al., 1991; Graff-Radford et al., 2019). Further study of DESH and disorders of CSF dynamics throughout the disease spectrum, including those who are asymptomatic in the community and patients with a clinical diagnosis of NPH, will help to better elucidate interactions of DESH with other predictors of cognitive decline. Of note, although ventriculomegaly, a component of DESH, has been shown to be associated with cognitive decline (Li et al., 2017), it was not individually studied, as it is nonspecific and may be due to neurodegeneration and atrophy or hydrocephalus with or without additional features of DESH.

Prior works evaluating the DESH score as a marker of disordered CSF dynamics and its associations with cognition are limited. In a prior cross-sectional study (Graff-Radford et al., 2019), the association of the DESH score with other imaging biomarkers and cognition was evaluated using a DESH score > 1 as the threshold for the presence of high convexity tight sulci and imaging features of disordered CSF dynamics. A DESH score of > 1 was present in about 7% of the participants in that MCSA study, and those participants had lower cortical thickness, higher WMH volume, and lower memory and attention z scores than those participants with a DESH score < 0. Based on this prior study and other prior work, the degree to which cognitive impairment in individuals with DESH was related to the inferred CSF dynamics disorder or co-existent pathology was unclear. In the current study we evaluated associations with the DESH score in a larger MCSA cohort, performed longitudinal evaluation, and considered the DESH score as a continuous variable in a model adjusted for other well-known predictors of cognitive decline with the goal to define the specific contribution of CSF dynamics to cognitive decline in the aging community population.

An association between DESH MRI features and cognition may be inferred in advanced CSF dynamics disorders based on the high prevalence of DESH in NPH and cognitive impairment being one of the cardinal clinical features of the syndrome (Hashimoto et al., 2010). The association of DESH with cognition in the less advanced disease spectrum of CSF dynamics disorders, such as may exist in the general population or community-based studies such as the MCSA, has not been well defined. In this work we showed that not only is DESH modestly associated with categorical progression from unimpaired to cognitive impairment, it is an independent risk factor for decline on continuous cognitive measures. Since DESH contributes to cognitive decline and is present in the general population, identifying individuals with DESH features may be important clinically and for selection in clinical trials.

Although CSF dynamics disorders have been under-appreciated in clinical and research setting, awareness is beginning to grow. Recent studies have shown the prevalence of DESH imaging features to be approximately 1-7% in community-based populations (Akiba et al., 2020; Graff-Radford et al., 2019, ; Hiraoka et al., 2008; Jaraj et al., 2014). Although less common than Alzheimer's disease or cerebrovascular disease, CSF dynamics disorders warrants consideration in evaluation of cognitive decline. DESH imaging features may be identified via visual interpretation or via automated methods, as used in this work. As automated determination of a DESH score requires volumetric imaging and processing tools, not widely available in the clinical setting, this method of detection may be best suited for research studies. Automated determination of a DESH score would be particularly useful in future studies with large numbers of participants, for which visual inspection would be time-consuming, and for scoring of DESH on a continuous scale, rather than as a binary variable. In the clinical setting, identification of DESH

imaging features will allow for consideration of disordered CSF dynamics as a contributor to cognitive decline and suggest investigation for additional clinical features of CSF dynamics disorders, which may be treated with CSF diversion. In the research setting, CSF dynamics disorders should be considered as co-pathology contributing to cognitive decline in some individuals, and in particular in selection for clinical trials as a contributor to cognitive decline that would not be addressed by disease-modifying treatments for Alzheimer's disease. Because CSF dynamics disorders are not widely appreciated, these individuals are routinely enrolled in Alzheimer's disease clinical trials (preclinical and symptomatic trials). CSF dynamics disorders will contaminate interpretation of results of these trials. Broader awareness of the impact of CSF dynamics disorders on cognition in elderly individuals is thus needed in the design and conduct of therapeutic trials.

Strengths of this study include the large size of the cohort and longitudinal analyses. There are also limitations. As described above, all cognitive domain z scores are not available for all participants. DESH is thought to be a marker of a CSF dynamics disorder that occurs on a spectrum. Although we anticipate findings to apply throughout the spectrum of CSF dynamics disorders, the automated DESH score algorithm we used here has yet to be applied to the more advanced disease spectrum.

In conclusion, we applied an automated algorithm to determine DESH scores, an indicator of tight high convexity sulci and a CSF dynamics disorder. The DESH score was shown to be an independent predictor of greater annual decline in all cognitive domain z scores and also showed evidence of being associated with greater rate of categorical progression from unimpaired to MCI or dementia. Although the effect size of the DESH score was less than that of other well-established predictors of cognitive decline (age, APOE, and cortical thickness), this study supports the presence of DESH in the community and demonstrates its presence to be an independent predictor of cognitive decline. Therefore, identifying individuals with DESH features may be important clinically as well as in clinical trial selection.

Funding

This work was supported by the National Institutes of Health [U01 AG006786, R37 AG011378, RO1 AG041851, R01 NS097495, and R01 AG056366]. The funding sources had no role in study design, analysis and interpretation or data, writing the manuscript, or the decision to submit the article for publication.

Data availability statement

Numeric data underlying these analyses may be made available to investigators upon reasonable request, via submission of a request to the MCSA executive committee.

Declaration of Competing Interest

C.R.J. serves on an independent data monitoring board for Roche and has consulted for Eisai, but he receives no personal compensation from any commercial entity. He receives research support from NIH and the Alexander Family Alzheimer's Disease Research Professorship of the Mayo Clinic.

D.T.J. receives funding from the NIH and the Minnesota Partnership for Biotechnology and Medical Genomics.

D.S.K. served on a Data Safety Monitoring Board for the DIAN study. He serves on a Data Safety Monitoring Board for a tau therapeutic for Biogen, but receives no personal compensation. He is an investigator in clinical trials sponsored by Biogen, Lilly Pharmaceuticals, and the University of Southern California. He serves as a consultant for Samus Therapeutics, Third Rock, and Alzeca Biosciences but receives no personal compensation. He receives research support from the NIH.

R.C.P. has consulted for Roche, Inc.; Merck, Inc.; Biogen, Inc.; Eisai, Inc. and is on a Data and Safety Monitoring Committee for Genentech, Inc. He receives research support from the National Institute on Aging, the GHR Foundation, and the Alzheimer's Association.

J.G-R. receives research support from the NIH.

C.G.S. receives research support from the NIH.

M.L.S. has owned shares of the following medical related stocks, unrelated to the current work: Align Technology, Inc., LHC Group, Inc., Mesa Laboratories, Inc., Natus Medical Incorporated, Varex Imaging Corporation, CRISPR Therapeutics, Gilead Sciences, Inc., Globus Medical Inc., Inovio Biomedical Corp., Ionis Pharmaceuticals, Johnson & Johnson, Medtronic, Inc., Parexel International Corporation.

P.M.C., J.L.G., H.J.W., and S.D.W. report no competing interests.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2021.117899.

References

Adams, R.D., Fisher, C.M., Hakim, S., Ojemann, R.G., Sweet, W.H., 1965. Symptomatic occult hydrocephalus with normal cerebrospinal-fluid pressure. N. Engl. J. Med. 273, 117–126. doi:10.1056/NEJM196507152730301.

Akiba, C., Gyanwali, B., Villaraza, S., Nakajima, M., Miyajima, M., Cheng, C.-Y., Wong, T.Y., Venketasubramanian, N., Hilal, S., Chen, C., 2020. The prevalence and clinical associations of disproportionately enlarged subarachnoid space hydrocephalus (DESH), an imaging feature of idiopathic normal pressure hydrocephalus in community and memory clinic based Singaporean cohorts. J. Neurol. Sci. 408, 116510. doi:10.1016/j.jns.2019.116510.

Alley, D., Suthers, K., Crimmins, E., 2007. Education and cognitive decline in older americans: results from the AHEAD sample. Res. Aging 29, 73–94. doi:10.1177/0164027506294245.

Au, R., Massaro, J.M., Wolf, P.A., Young, M.E., Beiser, A., Seshadri, S., D'Agostino, R.B., DeCarli, C., 2006. Association of white matter hyperintensity volume with decreased cognitive functioning: the framingham heart study. Arch. Neurol. 63, 246–250. doi:10.1001/archneur.63.2.246.

Bangen, K.J., Preis, S.R., Delano-Wood, L., Wolf, P.A., Libon, D.J., Bondi, M.W., Au, R., DeCarli, C., Brickman, A.M., 2018. Baseline white matter hyperintensities and hippocampal volume are associated with conversion from normal cognition to mild cognitive impairment in the Framingham Offspring Study. Alzheimer Dis. Assoc. Disord. 32, 50–56. doi:10.1097/WAD.0000000000000215.

Blacker, D., Albert, M.S., Bassett, S.S., Go, R.C., Harrell, L.E., Folstein, M.F., 1994. Reliability and validity of NINCDS-ADRDA criteria for Alzheimer's disease. the national institute of mental health genetics initiative. Arch. Neurol. 51, 1198–1204. doi:10.1001/archneur.1994.00540240042014.

Bradley, W.G., Whittemore, A.R., Watanabe, A.S., Davis, S.J., Teresi, L.M., Homyak, M., 1991. Association of deep white matter infarction with chronic communicating hydrocephalus: implications regarding the possible origin of normal-pressure hydrocephalus. AJNR Am. J. Neuroradiol. 12, 31–39.

Fiford, C.M., Sudre, C.H., Pemberton, H., Walsh, P., Manning, E., Malone, I.B., Nicholas, J., Bouvy, W.H., Carmichael, O.T., Biessels, G.J., Cardoso, M.J., Barnes, J.Alzheimer's Disease Neuroimaging Initiative, 2020. Automated white matter hyperintensity segmentation using bayesian model selection: assessment and correlations with cognitive change. Neuroinformatics doi:10.1007/s12021-019-09439-6.

Fischl, B., Dale, A.M., 2000. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc. Natl Acad. Sci. 97, 11050–11055. doi:10.1073/pnas.200033797.

Graff-Radford, J., Gunter, J.L., Jones, D.T., Przybelski, S.A., Schwarz, C.G., Huston, J., Lowe, V., Elder, B.D., Machulda, M.M., Gunter, N.B., Petersen, R.C., Kantarci, K., Vemuri, P., Mielke, M.M., Knopman, D.S., Graff-Radford, N.R., Jack, C.R., 2019. Cerebrospinal fluid dynamics disorders: Relationship to Alzheimer biomarkers and cognition. Neurology 93, e2237–e2246. doi:10.1212/WNL.0000000000008616.

Gunter, N.B., Schwarz, C.G., Graff-Radford, J., Gunter, J.L., Jones, D.T., Graff-Radford, N.R., Petersen, R.C., Knopman, D.S., Jack, C.R., 2019. Automated detection of imaging features of disproportionately enlarged subarachnoid space hydrocephalus using machine learning methods. Neuroimage Clin. 21, 101605. doi:10.1016/j.nicl.2018.11.015.

Hashimoto, M., Ishikawa, M., Mori, E., Kuwana, N., 2010. Diagnosis of idiopathic normal pressure hydrocephalus is supported by MRI-based scheme: a prospective cohort study. Cerebrospinal Fluid Res 7, 18. doi:10.1186/1743-8454-7-18.

Hiraoka, K., Meguro, K., Mori, E., 2008. Prevalence of idiopathic normal-pressure hydrocephalus in the elderly population of a Japanese rural community. Neurol. Med. Chir. (Tokyo) 48, 197–199. doi:10.2176/nmc.48.197, discussion 199-200.

Jack, C.R., Wiste, H.J., Weigand, S.D., Therneau, T.M., Lowe, V.J., Knopman, D.S., Gunter, J.L., Senjem, M.L., Jones, D.T., Kantarci, K., Machulda, M.M., Mielke, M.M., Roberts, R.O., Vemuri, P., Reyes, D.A., Petersen, R.C., 2017. Defining imaging biomarker cut points for brain aging and Alzheimer's disease. Alzheimers Dement 13, 205–216. doi:10.1016/j.jalz.2016.08.005.

Jaraj, D., Rabiei, K., Marlow, T., Jensen, C., Skoog, I., Wikkelsø, C., 2014. Prevalence of idiopathic normal-pressure hydrocephalus. Neurology 82, 1449–1454. doi:10.1212/WNL.0000000000000342.

Kitagaki, H., Mori, E., Ishii, K., Yamaji, S., Hirono, N., Imamura, T., 1998. CSF spaces in idiopathic normal pressure hydrocephalus: morphology and volumetry. AJNR Am. J. Neuroradiol. 19, 1277–1284.

Li, X., Ba, M., Ng, K.P., Mathotaarachchi, S., Pascoal, T.A., Rosa-Neto, P., Gauthier, S., 2017. Characterizing biomarker features of cognitively normal individuals with ventriculomegaly. Alzheimers Dement (Amst) 10, 12–21. doi:10.1016/j.dadm.2017.08.001.

Narita, W., Nishio, Y., Baba, T., Iizuka, O., Ishihara, T., Matsuda, M., Iwasaki, M., Tominaga, T., Mori, E., 2016. High-convexity tightness predicts the shunt response in idiopathic normal pressure hydrocephalus. AJNR Am. J. Neuroradiol. 37, 1831–1837. doi:10.3174/ajnr.A4838.

Petersen, R.C., 2004. Mild cognitive impairment as a diagnostic entity. J. Intern. Med. 256, 183–194. doi:10.1111/j.1365-2796.2004.01388.x.

Raz, L., Jayachandran, M., Tosakulwong, N., Lesnick, T.G., Wille, S.M., Murphy, M.C., Senjem, M.L., Gunter, J.L., Vemuri, P., Jack, C.R., Miller, V.M., Kantarci, K., 2013. Thrombogenic microvesicles and white matter hyperintensities in postmenopausal women. Neurology 80, 911–918. doi:10.1212/WNL.0b013e3182840c9f.

Roberts, R.O., Geda, Y.E., Knopman, D.S., Cha, R.H., Pankratz, V.S., Boeve, B.F., Ivnik, R.J., Tangalos, E.G., Petersen, R.C., Rocca, W.A., 2008. The mayo clinic study of aging: design and sampling, participation, baseline measures and sample characteristics. Neuroepidemiology 30, 58–69. doi:10.1159/000115751.

Rocca, W.A., Boyd, C.M., Grossardt, B.R., Bobo, W.V., Finney Rutten, L.J., Roger, V.L., Ebbert, J.O., Therneau, T.M., Yawn, B.P., St Sauver, J.L., 2014. Prevalence of multimorbidity in a geographically defined American population: patterns by age, sex, and race/ethnicity. Mayo Clin. Proc. 89, 1336–1349. doi:10.1016/j.mayocp.2014.07.010.

Schwarz, C.G., Gunter, J.L., Ward, C.P., Vemuri, P., Senjem, M.L., Wiste, H.J., Petersen, R.C., Knopman, D.S., Jack, C.R., 2017. The Mayo Clinic adult lifespan template: better quantificaiton across the life span. Alzheimer's Dementia 13, P93–P94. doi:10.1016/j.jalz.2017.06.2396.

Tilvis, R.S., Kähönen-Väre, M.H., Jolkkonen, J., Valvanne, J., Pitkala, K.H., Strandberg, T.E., 2004. Predictors of cognitive decline and mortality of aged people over a 10-year period. J. Gerontol. A Biol. Sci. Med. Sci. 59, M268–M274. doi:10.1093/gerona/59.3.M268.

Wang, Y.-L., Chen, W., Cai, W.-J., Hu, H., Xu, W., Wang, Z.-T., Cao, X.-P., Tan, L., Yu, J.-T.Alzheimer's Disease Neuroimaging Initiative, 2020. Associations of white matter hyperintensities with cognitive decline: a longitudinal study. J. Alzheimers Dis. 73, 759–768. doi:10.3233/JAD-191005.

Wilson, R.S., Hebert, L.E., Scherr, P.A., Barnes, L.L., Mendes de Leon, C.F., Evans, D.A., 2009. Educational attainment and cognitive decline in old age. Neurology 72, 460–465. doi:10.1212/01.wnl.0000341782.71418.6c.