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## Authors' contributions

| Name                   | Location                                                | Contribution                                                                                                               |
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**Ethical publication statement:** We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

# Association of Cognitive and Structural Correlates of Brain Aging and Incident Epilepsy. The Framingham Heart Study

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## Abstract

**Objectives:** Late-onset epilepsy has the highest incidence among all age groups affected by epilepsy and often occurs in the absence of known clinical risk factors like stroke and dementia. There is increasing evidence that brain changes contributing to epileptogenesis likely start years before disease onset, and we aim to relate cognitive and imaging correlates of subclinical brain injury to incident late-onset epilepsy in a large, community-based cohort.

**Methods:** We studied Offspring Cohort of the Framingham Heart Study participants 45 years or older, who were free of prevalent stroke, dementia, or epilepsy, and had neuropsychological (NP) evaluation and brain MRI. Cognitive measures included Visual Reproduction Delayed Recall, Logical Memory Delayed Recall, Similarities, Trail Making B-A (TrB-TrA) and a global measure of cognition derived from principal component analysis. MRI measures included total cerebral brain volume, cortical grey matter volume, white matter hyperintensities (WMHV) and hippocampal volume. Incident epilepsy was identified through review of administrative data and medical records. Cox proportional hazards regression models were used for the analyses. All analyses were adjusted for age, sex and educational level (cognition only).

**Results:** Among participants who underwent NP testing (n=2349, 41.26% male) 31 incident epilepsy cases were identified during follow-up. Better performance in TrB-TrA was associated with lower risk of developing epilepsy (HR [95%CI]:0.25[0.08, 0.73],p= 0.011). In the subgroup of participants with MRI (n=2056, 42.5% male), 27 developed epilepsy. Higher WMHV was associated with higher epilepsy risk (HR [95%CI]:1.5 [1.01, 2.20],p= 0.042), but higher CGMV (HR [95%CI]:0.73[0.57, 0.93],p= 0.001) was associated with lower incidence of epilepsy.

**Significance:** Better performance in TrB-TrA, a measure of executive function and attention, and higher cortical volumes are associated with lower risk of developing epilepsy. Conversely, higher WMHV, a measure of occult vascular injury, increases the risk. Our study shows that non-invasive tests performed in mid-life may help identify people at risk for developing epilepsy later in life.

## Keywords

epilepsy; elderly; neuroepidemiology; cognitive testing; MRI brain

## Introduction

Late-onset epilepsy (LOE) often is associated with stroke and dementia, but its cause remains unknown in ~30% of cases. Occult cerebrovascular disease contributes to higher incidence of epilepsy with increasing age<sup>1</sup>. Cognitive deterioration is a risk-factor and patient concern in LOE<sup>2, 3</sup>. Studies support cognitive impairments at and or before epilepsy onset<sup>4, 5</sup>. Faster cognitive decline occurs in prevalent and LOE with common comorbid conditions (e.g., vascular risk factors, metabolic disturbances, increased inflammatory response to seizures and polypharmacy) considered to accelerate brain aging<sup>4, 6</sup>.

Most structural and cognitive studies in LOE focus on prevalent epilepsy; few studies assessed long-term longitudinal data predating disease onset. Our study aims to investigate mid-life structural and neuropsychological measures of occult brain aging and link it to incident epilepsy later in life.

## Methods

### Study Population:

The Framingham Heart Study (FHS) is an ongoing prospective longitudinal, community-based study that began in 1948. In 1971, offspring of the Original Cohort and their spouses (n=5124) were enrolled in the Offspring Cohort (Gen 2) and have surveillance visits every 4 years. Gen 2 participants who attended their 7<sup>th</sup> clinic examination (1998–2001, n=3539), were invited to undergo a neuropsychological (NP) battery and magnetic resonance imaging (MRI) brain. Participants younger than 45 years of age and those with a history of stroke, dementia, epilepsy, or neurological conditions that could affect MRI measurements (eg, tumor, multiple sclerosis, significant traumatic brain injury, etc) were excluded (Figure 1).

### Cognitive function assessment:

A battery of NP tests to measure aspects of cognitive function associated with brain aging were administered using standard administration protocols by trained examiners. Our battery included Trail Making B minus A (TrB-TrA) (attention and executive function), Logical Memory Delayed Recall (LM-d) (verbal memory) and Visual Reproduction Delayed Recall (VR-d) (visual memory) from the Wechsler Memory Scale and the test of Similarities (verbal comprehension, reasoning, abstraction, and categorization) from the Wechsler Adult Intelligence Scale (WAIS). TrB-TrA were natural log-transformed to normalize their skewed distributions. We reversed the sign of TrB-TrA so that higher scores indicate superior

performance for all cognitive measures. Details of these tests administered in the FHS cohorts have been published previously<sup>7, 8</sup> Creation of a global cognitive score to reflect general cognitive ability involved calculating a general cognitive phenotype from 4 different cognitive tests. Principal component analysis was applied to the cognitive test scores to derive a general cognitive score by forcing a single-factor solution. Supplemental e-table 1 provides further details, including individual tasks used to create the global cognitive composite and their factor loadings<sup>9</sup>.

### **Volumetric Brain MRI:**

Four MRI measures of subclinical brain aging were used as predictors of incident epilepsy, namely total brain volume (TBV), a measure of overall (AD-type and vascular) brain aging, hippocampal volume (HV) which in older adults has been associated to AD-type pathology and is also an area of particular interest in temporal lobe epilepsy, white matter hyperintensities volume (WMHV), a measure of vascular brain injury also linked to late onset epilepsy<sup>1</sup>, and cortical grey matter volume (CGMV), decline of which has been linked to AD, other types of dementia, and is of specific interest in epilepsy, a disease primarily of the cortex. WMHV was natural logarithmically transformed to normalize skewed distributions. Details of brain MRI acquisition parameters, blinded analysis, definition of brain volumes and normative data for the FHS MRI dataset have been published recently<sup>10</sup>, and a summary may be found in the supplementary data (e-methods).

### **Epilepsy cases in the FHS:**

Our study's primary outcome was new epilepsy-onset during follow-up. The adjudication of epilepsy cases in the FHS was described<sup>11</sup> and includes a screening process followed by chart review to exclude seizure-mimics. Diagnosis consensus is reached by two epileptologists and cases are categorized according to the International League Against Epilepsy (ILAE) epidemiology commission recommendations (supplemental data: e-table 2)<sup>12</sup> For study purposes, epilepsy cases were defined as those participants meeting criteria for definite, probable and suspected epilepsy or single unprovoked seizure, similar to our prior publications<sup>11, 13</sup>.

### **Covariates:**

Vascular risk factors. Systolic and Diastolic blood pressures were calculated as the average of two seated resting measurements performed by a physician and hypertension was defined by the classification of the Seventh Report of the Joint National Committee (JNC VII) on Prevention, Detection, Evaluation, and Treatment of High Blood pressure (systolic blood pressure  $\geq 140$  mmHg and/or diastolic blood pressure  $\geq 90$  mmHg or use of anti-hypertensive (anti-HTN) medications). Diabetes mellitus was defined as a fasting blood glucose  $\geq 126$  mg/dl, a random blood glucose  $\geq 200$  mg/dl, previous diagnosis of DM or being on hypoglycemic medications or insulin. We used the total cholesterol/HDL ratio a continuous variable to assess hyperlipidemia. Current cigarette smoking was defined as self-reported regular at exam 7. Education level was analyzed as a binary variable "high school degree or less" and "beyond high school degree". Body mass index (BMI) was weight (in kilograms) divided by the square of height (in meters). Apolipoprotein E  $\epsilon 4$  allele (APOE $\epsilon 4$ ) genotyping was analyzed as an indicator of at least one<sup>14</sup>  $\epsilon 4$  allele. Physical

activity index (PAI) was constructed by weighting each hour in a participant's typical day based on self-reported activity level and summing these up over a 24-hours<sup>15</sup>. Lower PAI is linked to a higher risk of incident dementia<sup>16</sup>. Finally, depressive symptoms were assessed with the Center for Epidemiologic Studies Depression Scale (CESD) scores and analyzed using an indicator cutoff  $\geq 16$ .

### Statistical analyses:

We used Cox proportional hazards regression analyses to estimate Hazard ratios and 95% confidence intervals for the relation of exposures and LOE, adjusting for confounders selected based on published literature. The origin of the survival models was defined as the time of the MRI/NP acquisition. Survival time is defined as the time of event for those who had epilepsy, for those who died free of epilepsy it's the time to death and for others it's the censoring time until when participants are known to be free of epilepsy. We assessed proportionality of hazard using SCHOENFELD residual with model 1. A. Relation of NP data and incident epilepsy: Model 1 adjusted for age, sex, and education level; Model 2 additionally adjusted for systolic BP, treatment for HTN, DM, smoking, presence of APOE  $\epsilon 4$  allele, BMI, and total cholesterol/HDL ratio and Model 3 additionally adjusted for CESD score cutoff  $\geq 16$  and PAI. B. Relation of imaging data and incident epilepsy: Models 1–3 used the same variables as in models in A. except for exclusion of education level. Epilepsy follow-up was through 2016. In sensitivity analysis, we also looked at the association between all variables and epilepsy excluding suspected epilepsy/seizure cases. Following identification of significant associations between TrB-TrA, WMHV and CGMV to incident epilepsy, we performed further sensitivity analysis for these specific variables adjusting for age, sex and each of the covariates in model 2 and 3 separately. All results were considered statistically significant if  $p < 0.05$ . Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina).

### Standard Protocol Approvals, Registrations, and Patient Consents.

All protocols were approved by the Boston University Medical Center Institutional Review Board. All participants provide written informed consent when joining the FHS.

### Data availability statement:

All data collected on Framingham Study participants, including those used in our analysis, are available to qualified scientific investigators outside FHS who complete a research application, in accordance with FHS data sharing policies.

## Results

### Cohort Demographics

Table 1 and Table 2 summarize participants' characteristics at the time of NP testing and brain imaging, respectively. The time interval between MRI acquisition and NP testing was mean ( $\pm$  SD) of  $13.98 \pm 110$  days. NP testing was performed in 2,349 participants; 41.3% male, mean ( $\pm$ SD) age of  $62 \pm 9$  years. Participating individuals were slightly younger, of higher educational status and with a lower prevalence of vascular risk factors compared to those who did not have NP (supplemental data: e-table 3). APOE  $\epsilon 4$  allele was present

in 20.1% and the majority had at least some education beyond high school. In this group there were 31 incident epilepsy cases captured (definite 18, probable 7, suspected 6) over mean( $\pm$ SD) 7.10 $\pm$ 3.44 years from NP testing. The overall crude incidence of epilepsy in our sample of 2,349 participants was 0.97 per 1000 patient-years. Among the 2,056 participants (42.57% male) who also had a brain MRI (mean age 62 $\pm$ 9 years with APOE $\epsilon$ 4 allele present in 20.9%) there were 27 incident epilepsy cases captured (definite 15, probable 6, suspected 6) over mean( $\pm$ SD) 7.04 $\pm$ 3.38 years from MRI acquisition.

### Cognitive function and risk of incident epilepsy

In multivariable analyses in model 1, better performance in TrB-TrA was associated with lower risk of subsequent LOE (HR 0.25, 95%CI [0.08,0.73],  $p=0.011$ ) (Table 3). There was no association with performance on tests of LM-d, VR-d, Similarities, global cognitive score and LOE. Additional adjustments in Model 2 did not change the associations observed, but in model 3, the association was attenuated and no longer significant. In sensitivity analysis looking at each covariate included in models 2 and 3 separately, significance was lost only when adjusting for PAI (supplemental data: e-table 4).

### Cerebral volumes and risk of incident epilepsy

In the primary model, we observed a significant association between higher WMHV and increased epilepsy risk (HR [95% CI]: 1.5 [1.01, 2.20],  $p=0.042$ ). While there was a similar modest association after adjustment in models 2 and 3, it was no longer statistically significant (Table 4). In sensitivity analysis looking at each covariate included in models 2 and 3 separately, the effect size remained very similar, but significance was lost when adjusting for participants receiving hypertension treatment, for BMI and for PAI (supplemental data: e-table 5).

In the primary model higher CGMV was associated with lower risk of incident epilepsy (HR [95% CI]: 0.73 [0.57, 0.93],  $p=0.001$ ) an association that remained significant across all 3 Models (Table 4) and when adjusting for each covariate separate (supplemental data: e-table 6)

When we used a stricter definition of epilepsy excluding suspected epilepsy and suspected single unprovoked seizures similar associations were observed using models 1–3. Among 2317 participants who had NP, 24 developed epilepsy and better performance in TrB-TrA was associated with lower risk of developing epilepsy (HR [95%CI]: 0.2 [0.06, 0.62],  $p=0.005$ .(supplemental data: e-table 7) In the subgroup of participants with MRI, higher WMHV was associated with higher epilepsy risk (HR [95%CI]: 1.78 [1.12, 2.70],  $p=0.014$ ), and higher CGMV (HR [95%CI]: 0.73 [0.56, 0.96],  $p=0.024$ ) was associated with lower incidence of epilepsy (supplemental data: e-table 8).

## Discussion

Our population-based study showed that better performance in TrB-TrA, a measure of executive function and attention, and higher cortical volumes, both measured in midlife in individuals free of clinical stroke or dementia, were associated with lower risk of incident

LOE. By contrast, higher WMHV, a measure of subclinical vascular brain injury, increased the risk.

### Cognitive function and risk of incident epilepsy

Population-based studies found an increased rate of cognitive decline predating and following LOE (onset > age 67)<sup>4</sup>, as well as among older individuals (>65 years) with prevalent epilepsy, especially with an APOE ε4 allele<sup>6</sup>. Domains studied included global cognitive function, executive function and verbal memory. Further analysis showed that older adults with epilepsy who also had hypertension or abstained from alcohol (compared to moderate use) experienced a faster global cognitive decline than what is expected for age or epilepsy alone<sup>4,17</sup>. However, abstinence from alcohol may be a behavioral choice to prevent seizures. Executive function deficits were described among older individuals (mean age 70) with new onset epilepsy before initiating anti-seizure drugs (ASDs); dysfunction was more pronounced in those with prior stroke, neurologic comorbidities, and high BMI<sup>18</sup>. Impaired attention and executive function are linked to vascular brain injury and is the most pronounced deficit among those with poststroke cognitive decline<sup>19</sup> and periventricular WMH and lacunar infarcts<sup>20</sup>. Therefore, our findings that focus on the period predating the clinical development of epilepsy point to a primarily vascular dysfunction as an early predictor of incident LOE. Among the 31 participants in our study who developed epilepsy only two interim strokes were captured which further suggests vascular dysfunction may be relevant even in the absence of an overt stroke. The lack of association with other cognitive measures in our study may reflect differences in design (we did not assess cognitive changes over time), in the populations studied, and in the presence and type of epilepsy at the time of the cognitive testing. Memory deficits, for example, that reflect hippocampal dysfunction, are more frequent in older patients with prevalent temporal lobe epilepsy (TLE) of either early or late-onset<sup>21</sup>, suggesting that hippocampus-dependent memory impairment is accelerated after epilepsy onset. This was not assessed in our study.

### Cerebral volumes and risk of incident epilepsy

Our findings replicate the ARIC Study<sup>1</sup> where increased WMHV measured in midlife (mean age 64) was associated with an increased rate of LOE with a HR of 1.27, similar to our HR of 1.5. In that study, a cross-sectional association was seen between lower cortical volumes and LOE at a second MRI obtained when the participants were older (mean age 78). Our study expands those observations to include midlife cortical grey matter volume as a predictor of subsequent epilepsy.

Most structural studies focused on prevalent epilepsy. Few studies assessed structural changes and LOE. In one, prevalent LOE was linked to increased WMHV and cortical atrophy compared to controls<sup>22</sup>, but another one among slightly older individuals with LOE, WMHV was similar to healthy controls and less than in patients with TIA or lacunar strokes. Associations with WMHV may become attenuated with increasing age, as white matter changes become increasingly more prevalent<sup>23</sup>. One study on unknown etiology late-onset TLE in Japan showed significant gray matter increases in the bilateral amygdala and anterior hippocampus and no significant differences from controls in white matter volume<sup>24</sup>. Amygdala enlargement can occur in TLE, but its pathological significance

remains controversial and raise the possibility of an inflammatory process in elderly patients. When considering studies that address structural changes across the lifespan in epilepsy, increased WMHV was found in patients with chronic and new-onset epilepsy versus controls<sup>25</sup>. Refractoriness of disease is another parameter that may contribute to structural changes and is associated with structural brain changes consistent with premature brain aging<sup>26</sup>. The large cross-sectional multicenter ENIGMA study with younger and diverse epilepsy patients, observed widespread patterns of altered subcortical volume and reduced cortical grey matter thickness, suggesting that some structural and genetic pathways may be shared across heterogeneous syndromes<sup>27</sup>. Our findings suggest that extensive cortical and subcortical changes likely predate clinical LOE. WMHV is affected by age and cerebrovascular risk factors as well as genetic influence even in middle age when symptomatic cerebrovascular disease is uncommon<sup>28</sup>. White matter lesions may interrupt prefrontal subcortical loops, impairing prefrontal lobe function and leading to neuronal loss in cortical associative areas as Wallerian degeneration may contribute to cognitive decline and generalized atrophy<sup>20</sup>. Further, increased WMHV is associated with an increased risk of amnesic mild cognitive impairment and dementia independent of vascular risk factors or interim stroke suggestive of additional mechanisms to atherosclerosis like AD-related pathological changes;<sup>29</sup> thus, a strict dichotomy between microvascular disease and neurodegeneration is inappropriate<sup>30</sup>. These observations converge in an epileptogenesis model centered around the neurovascular unit, a complex functional and multi-cellular structure. Dysfunction can result from interrelated processes including changes in cerebral blood flow, increased blood-brain-barrier permeability, and increased inflammation, as well as misfolded amyloid beta and tau protein accumulations<sup>31–34</sup>.

Data support that epileptogenesis in LOE likely extends beyond the seizure focus and involves subcortical and cortical regions. Our and others' observations support that these changes likely predate disease onset.

### Strengths and limitations

Strengths of this study include our large population-based sample, prospective data collection, detailed cognitive assessment using multiple tests, and extensive MRI cerebral volume data that reflect different potential mechanisms of brain aging. We systematically identified all epilepsy cases over an 18-year follow-up period. The replication of results in sensitivity analysis following exclusion of suspected cases, as outlined above, supports our a priori decision to include these cases in the analysis in our attempt to capture the entire spectrum of the disease in a community setting. In addition, we adjusted for many confounders, including vascular and dementia risk factors as well as lifestyle parameters. However, there were several limitations. First, there were few incident epilepsy cases which precluded further analysis on specific seizure types and in certain secondary models of our analysis (tables 3, 4 and e-tables 3–5) the low number of targeted events in combination to missing data for certain covariates may have lacked power and increased the type 1 error probability. Our study was observational which limits conclusions about the causality of the associations. Lastly, our study participants were mainly white individuals of European ancestry, limiting the generalizability of our findings to other races/ethnicities.

In conclusion, our study underlines specific cognitive domain deficits and structural changes that occur early in the epileptogenesis of LOE prior to onset of clinical seizures and may help identify middle-aged individuals at risk of developing LOE with the use of non-invasive methods. Further studies are needed to define the role of genetics, inflammation, amyloid and tau accumulation in seizure generation and whether aggressive management of vascular risk factors or other treatment options (ASDs, agents against neurodegeneration) can make a difference. It is apparent that early intervention will be essential in lowering the prevalence of LOE in an aging population.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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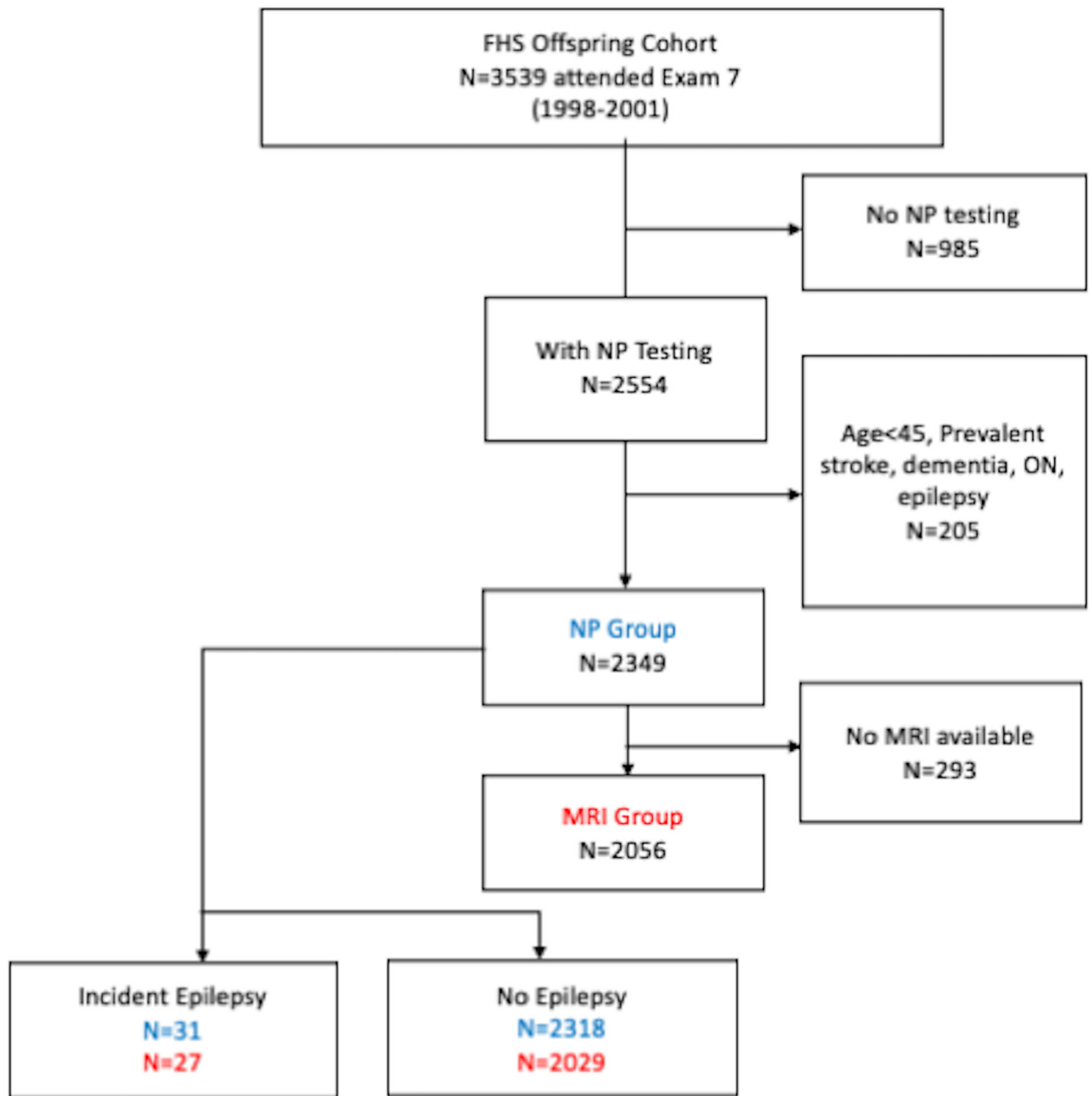
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**Key Points**

Participants performing better in TrB-TrA, an attention and executive function test, and those with higher cortical volumes, had a lower risk of epilepsy.

Participants with higher WMHV, a measure of occult vascular injury, had increased risk of epilepsy.

Non-invasive cognitive and imaging tests performed in mid-life may help identify people at risk for developing epilepsy later in life.



NP: neuropsychological, MRI: Magnetic Resonance Imaging, ON: Other Neuro (neurological conditions associated with structural abnormalities)

**Figure 1.**  
NP/MR Epilepsy Sample Selection Flowchart

**Table 1.**

Characteristics of participants with NP data

|                                                               | Overall (N=2349)                          |
|---------------------------------------------------------------|-------------------------------------------|
| Age, years                                                    | 62 (8.81)                                 |
| Male, n (%)                                                   | 1076 (41.26)                              |
| Systolic Blood Pressure, mg/dL                                | 126 (18.55)                               |
| Body Mass Index, Kg/m <sup>2</sup>                            | 27.44 [24.5, 30.7]                        |
| Education, n (%)                                              |                                           |
| No High School Degree                                         | 86 (3.30)                                 |
| High School Degree                                            | 653 (25.04)                               |
| Some College                                                  | 714 (27.38)                               |
| College Graduate                                              | 896 (34.36)                               |
| High School Degree or less                                    | 739 (28.34)                               |
| Physical Activity Index Score                                 | 38 (6.35)                                 |
| Current smoking, n (%)                                        | 286 (10.97)                               |
| Hypertension Treatment, n (%)                                 | 731 (28.10)                               |
| Diabetes Mellitus, n (%)                                      | 267 (10.87)                               |
| APOE 4, n(%)                                                  | 511 (20.11)                               |
| Depression score (CESD>=16), n(%)                             | 192 (8.29)                                |
| Follow-up time, years; mean (SD); Median [Q1, Q3]; (min, max) | 13.64 (3.31); 15.00 [13.0, 16.0]; (1, 17) |
| *Global Cognitive Score                                       | -0.01 (1.00); 0.09 [-0.61, 0.68]          |
| *Trail Making Test A                                          | 0.54 (0.22); 0.50 [0.40, 0.62]            |
| *Trail Making Test B                                          | 1.43 (1.05); 1.20 [0.93, 1.58]            |
| *Trail Making Test B minus A                                  | 0.88 (0.97); 0.67 [0.45, 1.00]            |
| *Logical Memory Delayed Recall                                | 10.54 (3.60); 11.00 [8.00, 13.00]         |
| *Visual Delayed Recall                                        | 8.11 (3.36); 8.00 [6.00, 11.00]           |
| *Similarities                                                 | 16.71 (3.59); 17.00 [15.00, 19.00]        |

Values are mean (SD), n (%),

\* mean (SD); Median [Q1, Q3]

\*\*\* Values are mean (SD), row percent

**Table 2.**

Characteristics of participants with MRI brain

|                                                              | Overall (N=2056)                          |
|--------------------------------------------------------------|-------------------------------------------|
| Age, years                                                   | 62 (8.83)                                 |
| Male, n (%)                                                  | 946 (42.57)                               |
| Systolic Blood Pressure, mg/dL                               | 126 (18.51)                               |
| Body Mass Index, Kg/m <sup>2</sup>                           | 27.33 [24.3, 30.6]                        |
| Education, n (%)                                             |                                           |
| No High School Degree                                        | 69 (3.11)                                 |
| Up to High School Degree                                     | 566 (25.47)                               |
| Some College                                                 | 621 (27.95)                               |
| College Graduate                                             | 800 (36.00)                               |
| Physical Activity Index Score                                | 38 (6.33)                                 |
| Current smoking, n (%)                                       | 247 (11.12)                               |
| Hypertension Treatment, n (%)                                | 625 (28.19)                               |
| Diabetes Mellitus, n (%)                                     | 237 (11.10)                               |
| APOE 4, n (%)                                                | 452 (20.85)                               |
| Depression score (CESD16+), n (%)                            | 161 (7.94)                                |
| Survival time, years; mean (SD); Median [Q1, Q3]; (min, max) | 13.69 (3.32); 15.00 [13.0, 16.0]; (1, 17) |
| *Total Brain Volume                                          | 77.48 (2.49); 77.76 [75.91, 79.28]        |
| *Hippocampal Volume                                          | 0.53 (0.05); 0.53 [0.50, 0.56]            |
| *White Matter Hyperintensity Volume                          | 0.08 (0.20); 0.04 [0.02, 0.07]            |
| *Cortical Grey Matter Volume                                 | 38.41 (1.70); 38.49 [37.29, 39.55]        |

Values are mean (SD), n (%),

\* Expressed as a percentage of intracranial volume, mean (SD), Median [Q1, Q3]

**Table 3.**

Association between NP and incidence of Epilepsy

| Marker                             | Number of events / N | HR [95% CI], p-value            |
|------------------------------------|----------------------|---------------------------------|
| Global Cognitive Score             |                      |                                 |
| Model 1                            | 30/2323              | 0.84 [0.55, 1.29], 0.428        |
| Model 2                            | 28/2155              | 0.89 [0.57, 1.37], 0.591        |
| Model 3                            | 25/2017              | 0.99 [0.61, 1.62], 0.985        |
| Trail Making Test B minus A        |                      |                                 |
| Model 1                            | 30/2323              | <b>0.25 [0.08, 0.73], 0.011</b> |
| Model 2                            | 28/2155              | <b>0.31 [0.10, 0.95], 0.040</b> |
| Model 3                            | 25/2017              | 0.44 [0.11, 1.76], 0.244        |
| Logical Memory Delayed Recall      |                      |                                 |
| Model 1                            | 31/2347              | 0.96 [0.87, 1.07], 0.474        |
| Model 2                            | 29/2175              | 0.96 [0.86, 1.06], 0.435        |
| Model 3                            | 26/2034              | 0.98 [0.88, 1.09], 0.732        |
| Visual Reproduction Delayed Recall |                      |                                 |
| Model 1                            | 31/2345              | 0.92 [0.82, 1.03], 0.140        |
| Model 2                            | 29/2174              | 0.94 [0.83, 1.06], 0.313        |
| Model 3                            | 26/2034              | 0.96 [0.84, 1.09], 0.504        |
| Similarities                       |                      |                                 |
| Model 1                            | 31/2349              | 1.04 [0.93, 1.16], 0.487        |
| Model 2                            | 29/2177              | 1.04 [0.92, 1.16], 0.529        |
| Model 3                            | 26/2036              | 1.02 [0.90, 1.15], 0.782        |

Model 1 adjusted for age, sex, and education.

Model 2 In addition, adjusted for systolic BP, treatment for HTN, DM, smoking, APOE 4, BMI, and total cholesterol/HDL ratio.

Model 3 adjusted for Model 2 plus depression score and physical activity index.

**Table 4.**

Association between MRI and incidence of Epilepsy

| Marker                             | Number of events / N | HR [95% CI], p-value            |
|------------------------------------|----------------------|---------------------------------|
| Total Brain Volume                 |                      |                                 |
| Model 1                            | 27/2056              | 0.86 [0.71, 1.05], 0.143        |
| Model 2                            | 25/1926              | 0.87 [0.71, 1.07], 0.195        |
| Model 3                            | 22/1809              | 0.85 [0.69, 1.06], 0.162        |
| Hippocampal Volume                 |                      |                                 |
| Model 1                            | 27/2056              | 0.002 [0.001, 8.55], 0.148      |
| Model 2                            | 25/1926              | 0.003 [0.001, 20.33], 0.196     |
| Model 3                            | 22/1809              | 0.006 [0.001, 83.38], 0.292     |
| White Matter Hyperintensity Volume |                      |                                 |
| Model 1                            | 27/2023              | <b>1.49 [1.01, 2.20], 0.042</b> |
| Model 2                            | 25/1904              | 1.47 [0.98, 2.22], 0.065        |
| Model 3                            | 22/1788              | 1.45 [0.93, 2.25], 0.099        |
| Cortical Gray Matter Volume        |                      |                                 |
| Model 1                            | 27/2056              | <b>0.73 [0.57, 0.93], 0.001</b> |
| Model 2                            | 25/1926              | <b>0.74 [0.58, 0.95], 0.017</b> |
| Model 3                            | 22/1809              | <b>0.75 [0.58, 0.99], 0.042</b> |

Model 1 adjusted for age and sex

Model 2 In addition, adjust for systolic BP, treatment for HTN, DM, smoking, APOE 4, BMI, and total cholesterol/HDL ratio

Model 3 adjusted for Model 2 plus Depression score and physical activity index