Hippocampal Atrophy and Subsequent Depressive Symptoms in Older Men and Women: Results From a 10-Year Prospective Cohort

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Several studies have reported smaller hippocampal volume in patients with depression. However, the temporality of the association is undetermined. One hypothesis is that hippocampal atrophy might be a susceptibility factor for depression. In the present study, we assessed whether hippocampal atrophy was associated with subsequent depressive symptoms in a cohort of older French adults (n=1,309) who were 65–80 years of age and enrolled into the study in 1999–2001 in Dijon, France. Subjects were followed for more than 10 years. Participants underwent 2 cerebral magnetic resonance imaging scans, one at baseline and one at the 4-year follow-up. We used linear mixed models to estimate the associations of hippocampal atrophy with 1) the average depressive symptom scores over follow-up (using the Center for Epidemiologic Studies-Depression scale) measured biennially over the subsequent 6 years and 2) changes in symptom scores over follow-up. In women, a 2-standard-deviation increase in annual hippocampal atrophy was associated with a 1.67-point (95% confidence interval: 0.59, 2.77) increase in the average depressive symptom score over follow-up and with a 1.97-point (95% confidence interval: 0.68, 3.24) increase in scores over the 2 subsequent years but not with later changes in symptoms. No association was detected in men. Accounting for potential selective attrition (using inverse probability weights) did not alter results. Hippocampal atrophy was associated with more subsequent depressive symptoms and with shorter-term worsening of symptoms in women.

Abbreviations: CES-D, Center for Epidemiologic Studies-Depression scale; CI, confidence interval; HcV, hippocampal volume; IPW, inverse probability weight; MRI, magnetic resonance imaging.
In older adults, depressive symptoms are common, can persist for years (17, 18), and have been linked to multiple adverse outcomes, including functional impairment, cognitive decline, cardiovascular morbidities, and death (19–21). In addition, older adults may be more susceptible to severe consequences of hippocampal shrinkage. The neurocognitive consequences of hippocampal atrophy have largely been described (22–24), whereas less is known about the link between hippocampal atrophy and depressive symptoms. In the present study, we assessed whether hippocampal atrophy was associated with subsequent depressive symptoms measured over 6 years in a population-based cohort of older adults.

METHODS

Study population

The Three-City Study, a French population-based prospective study of older adults, has been described in detail previously (25). Between January 1999 and March 2001, a total of 9,294 participants who were 65 years of age or older and not institutionalized were randomly selected from electoral rolls of the cities of Bordeaux (n = 2,104), Dijon (n = 4,931), and Montpellier (n = 2,259). The study protocol was approved by the Ethics Committee of the University Hospital of Kremlin-Bicêtre. All participants signed an informed consent.

We report results from the Dijon cohort, in which brain MRI examinations were performed (Three-City Dijon MRI Study). At baseline, an MRI was proposed to all subjects who were 65–80 years of age and enrolled into the study between 1999 and 2000 (n = 2,763); 2,285 (83%) subjects agreed to participate. Because of financial restrictions, only 1,924 baseline scans were performed; of those, 1,806 yielded valid HcV measurements. We excluded 8 subjects with prevalent dementia and 23 participants who were older than 80 years at baseline (as per the original MRI substudy inclusion criteria), which resulted in a sample of 1,775 subjects with baseline HcV measurement. Follow-up waves were every 2 years on average. At the 4-year follow-up (wave 2), 1,328 (75%) of those subjects had a second MRI with valid HcV measurement. Of the 447 subjects without a second MRI, 49 were deceased before wave 2, 111 had poor-quality scans, and 287 refused or were not offered a second MRI (because of time constraints in access to the MRI scanner). On average, these subjects were older and had smaller HcV, more depressive symptoms, and poorer cognitive functioning at baseline (data not shown).

We further eliminated 19 subjects who had missing information on relevant covariates (cognitive functioning, diabetes status, alcohol consumption, and total intracranial volume). Our final analytic sample, referred to as the “Three-City Study Dijon MRI sample,” included 1,309 subjects with 2 valid HcV measurements and complete information on potential confounders. These subjects were followed for up to 6 years (waves 3–5) after the second HcV measurement. The timeframe of the study sample is presented in Figure 1.

Depressive symptoms

The outcomes were depressive symptoms measured biennially from wave 2 (concomitant with the second MRI) through wave 5, using the Center for Epidemiologic Studies-Depression scale (CES-D) (26). The CES-D includes 20 self-report items about feelings and symptoms experienced during the preceding week, with higher scores indicating more depressive symptoms; its suitability for measuring depressive symptoms in older adults has been established, including in the French population (27). It was administered by trained psychologists in standardized face-to-face interviews at the subjects’ homes or at the study center. Total CES-D scores were obtained using item scoring according to the method proposed by Radloff (26); if data on 4 or more items were missing, the total CES-D score was considered missing (6 of 1,112 participants seen at wave 3 and 13 of 745 participants seen at wave 5).

Hippocampal atrophy

Baseline and wave 2 MRIs were performed using the same scanner (1.5 Tesla Magnetom; Siemens, Erlangen, Germany) and analyzed using identical procedures, as described previously (25, 28, 29). Tissue segmentation and brain tissue probability maps were obtained through an automated and validated procedure based on an optimized Voxel-Based Morphometry protocol using the Statistical Mapping Software (http://www.fil.ion.ucl.ac.uk/spm/). The Voxel-Based Morphometry protocol using the Statistical Mapping Software (http://www.fil.ion.ucl.ac.uk/spm/).

![Table 1. Timeframe of study sample and data collection, Three-City Dijon MRI Study, Dijon, France, 1999–2011. Highlighted are the predictor of interest, the hippocampal volume (HcV) atrophy computed using the 2 magnetic resonance imaging (MRI) examinations conducted 4 years apart, and the Center for Epidemiologic Studies-Depression scale (CES-D) scores collected at second MRI and over subsequent waves of follow-up. The 1,309 subjects with 2 complete MRI scans and valid HcV measurements constituted the final analytical sample; those not seen over follow-up waves (wave 3–wave 5) include those who refused follow-up and those who were lost to follow-up.](https://academic.oup.com/aje/article-abstract/180/4/385/2739146)
Hippocampal Atrophy and Depressive Symptoms

Protocol was modified to account for characteristics of older brains (30) and complemented with a modulation step (31). Gray matter, white matter, and cerebrospinal fluid volumes were computed as the integral of the voxel intensities of the modulated tissue partition image. Total intracranial volume was computed as the sum of gray matter, white matter, and cerebrospinal fluid volumes. Gray matter volumes in specific regions of interest were automatically computed by integrating the voxel intensities of the modulated partition images within each region (29, 32). Anatomical limits of the regions of interest were derived through macroscopic neuroanatomical parcellation (32), based on the high-resolution single-subject T1-volume provided by the Montreal Neurological Institute (33). In our analyses, the region of interest was total HcV (sum of left and right regions). The predictor of interest was the rate of change in HcV, expressed as the annualized percent change (22, 29) and computed as the change between baseline and follow-up HcV (relative to baseline HcV) divided by the individual delay in years between scans, as follows:

\[
\frac{(HcV_{T0} - HcV_{T2})}{HcV_{T0}(T2 - T0)} \times 100.
\]

Positive values indicate HcV loss (to which we will henceforth refer as atrophy); higher (positive) values correspond to faster rates of atrophy.

Statistical analyses

We used random-intercept multivariable linear mixed models (34) to assess the temporal relationships between HcV atrophy and change in subsequent depressive symptoms. Given the statistically significant \((P < 0.05)\) 2-way interaction between hippocampal atrophy and sex in the initial models, all analyses were performed separately for women and men. To account for within-subject correlations of consecutive CES-D scores, we used the heterogeneous autoregressive order 1 covariance structure (35). To account for longitudinal within-subject changes in depressive symptoms, we included binary indicators of study waves (wave 3–wave 5), which improved model fit (reduced Akaike’s information criterion (36)) compared with models that assumed linear changes over time (data not shown).

Two mixed-models were estimated. Model 1 estimated the adjusted association between HcV atrophy and average CES-D scores over follow-up measurements (wave 3–wave 5); it assumed that the association was constant over follow-up and adjusted for CES-D scores at wave 2 (measured concurrently with the second HcV) to assess whether hippocampal atrophy could predict subsequent depressive symptoms, even among subjects with the same CES-D score at wave 2. Model 2 estimated whether the association between HcV atrophy and CES-D scores changed across follow-up waves. This model used the CES-D at wave 2 as an additional measurement of the outcome and included interactions between atrophy and indicators of follow-up waves (wave 3–wave 5); the interaction terms tested whether changes in CES-D scores between wave 2 and a specific follow-up wave of interest (wave 3–wave 5) varied between subjects with different HcV atrophy. On the basis of model 2, we plotted the estimated changes over time in mean CES-D scores for subjects in the highest quartile of hippocampal atrophy versus those in the 3 lower quartiles.

To facilitate the interpretation of the results, we report for both mixed models the coefficients of associations corresponding to a more clinically relevant contrast based on a 2-standard-deviation increase in the annualized rate of hippocampal atrophy. Both mixed models adjusted for baseline values (at first HcV assessment) of a priori–selected potential confounders: age, educational level (≤primary school, technical/intermediate school, or ≥secondary school), body mass index (weight (kg)/height (m)^2), alcohol use (never, past, or current), presence of hypertension (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or reported use of antihypertensive medication), smoking status (former, current, or never smoker), history of cardiovascular/cerebrovascular conditions (any of the following: myocardial infarction, stroke, coronary surgery, angioplasty, or peripheral vascular diseases), self-reported diabetes mellitus status, cognitive functioning (assessed using the Mini-Mental State Examination (37)), and a binary time-varying indicator of place of study visit (home or study center). Use of baseline confounder values, measured before hippocampal atrophy assessment, avoided the risk of unwarranted adjustments for changes in covariates that could be on intermediate pathways between atrophy and depressive symptoms. In sensitivity analyses, we adjusted for time-varying values of cognitive functioning, hypertension, and diabetes.

In longitudinal cohorts of older adults, selective survival or attrition may lead to biased estimates (38–40). By the last study wave, 31% of our sample had dropped out and another 13% had died. These subjects had faster HcV atrophy and more depressive symptoms at wave 2 than did other participants (Web Table 1, available at http://aje.oxfordjournals.org/). We accounted for selective attrition using 2 approaches. First, in longitudinal analyses with missing outcome measures, mixed models generate likelihood-based estimates that are unbiased under the “missing at random” assumption (41) (provided that there is adjustment for variables that predict missingness). Because the main predictors of attrition in the Three-City Study Dijon MRI sample (age, HcV atrophy, wave 2 CES-D scores, cognitive functioning, diabetes, and hypertension) were all selected a priori as covariates in the mixed models, our analyses should not be affected by major selection biases. Secondly, in sensitivity analyses, we used inverse probability weights (IPWs) to further account for nonrandom censoring because of loss to follow-up or death (39, 42, 43). The IPWs allow for the adjustment of probable intermediate factors (e.g., cognitive and CES-D scores at earlier visits) while avoiding the potential pitfalls of conventional adjustment for these factors. For each subject at each study wave, the stabilized IPWs (44) were calculated by multiplying separate weights related to the probability of death and loss to follow-up and were then used to reweigh individual observations in the mixed-model analyses. Details of IPWs estimation are given in the Web Appendix. Statistical analyses were conducted using SAS software, version 9.2 (SAS Institute, Inc., Cary, North Carolina).
RESULTS

Table 1 presents the descriptive characteristics of the analytic sample at study entry (first HcV assessment). The mean age was 72 (standard deviation, 3.9) years; 62% of participants were women. The annual change in HcV was normally distributed, with a mean volume loss per year of 1.15% (standard deviation, 1.06) in women and 0.93% (standard deviation, 1.17) in men. Age-adjusted hippocampal atrophy was faster in women ($P = 0.001$). Mean CES-D scores and changes in scores across follow-up are summarized in Table 2. At each wave, women had higher scores ($P < 0.0001$).

Table 3 presents results from unweighted and weighted mixed model 1 and model 2. The reported coefficients for HcV atrophy correspond to a 2-standard-deviation increase in the annualized rate of atrophy (a 2-standard-deviation increase equals a 2.12% annual loss in HcV in women and a 2.34% loss in men).

Table 1. Characteristics at Study Entry and Hippocampal Volume Measurements of the Analytic Sample ($n = 1,309$), Three-City Dijon MRI Study, Dijon, France, 1999–2001

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Women ($n = 814$)</th>
<th></th>
<th>Men ($n = 495$)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>No. %</td>
<td>Mean (SD)</td>
<td>No. %</td>
</tr>
<tr>
<td>Demographic characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>72.03 (3.90)</td>
<td></td>
<td>71.81 (3.93)</td>
<td></td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school or lower</td>
<td>290 (35.63)</td>
<td></td>
<td>132 (26.67)</td>
<td></td>
</tr>
<tr>
<td>Intermediate/technical school</td>
<td>271 (33.29)</td>
<td></td>
<td>134 (27.07)</td>
<td></td>
</tr>
<tr>
<td>Secondary school or higher</td>
<td>253 (31.08)</td>
<td></td>
<td>229 (42.26)</td>
<td></td>
</tr>
<tr>
<td>Other health characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td>24.85 (3.78)</td>
<td></td>
<td>26.02 (3.32)</td>
<td></td>
</tr>
<tr>
<td>History of cardiovascular or cerebrovascular conditions</td>
<td>22 (2.70)</td>
<td></td>
<td>51 (10.30)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>570 (70.02)</td>
<td></td>
<td>417 (84.24)</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>674 (82.80)</td>
<td></td>
<td>150 (30.03)</td>
<td></td>
</tr>
<tr>
<td>Previous smoker</td>
<td>112 (13.76)</td>
<td></td>
<td>302 (61.01)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>28 (3.44)</td>
<td></td>
<td>43 (8.69)</td>
<td></td>
</tr>
<tr>
<td>Self-reported history of diabetes mellitus</td>
<td>46 (5.65)</td>
<td></td>
<td>48 (9.70)</td>
<td></td>
</tr>
<tr>
<td>MMSE score</td>
<td>27.75 (1.70)</td>
<td></td>
<td>27.86 (1.58)</td>
<td></td>
</tr>
<tr>
<td>Alcohol use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never use</td>
<td>17 (2.09)</td>
<td></td>
<td>6 (1.21)</td>
<td></td>
</tr>
<tr>
<td>Previous use</td>
<td>208 (25.55)</td>
<td></td>
<td>32 (6.46)</td>
<td></td>
</tr>
<tr>
<td>Current use</td>
<td>589 (72.36)</td>
<td></td>
<td>457 (92.32)</td>
<td></td>
</tr>
<tr>
<td>Cerebral MRI markers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline total intracranial volume, cm$^3$</td>
<td>1,305.38 (96.21)</td>
<td></td>
<td>1,479.21 (115.39)</td>
<td></td>
</tr>
<tr>
<td>Baseline HcV, cm$^3$</td>
<td>6.44 (0.73)</td>
<td></td>
<td>7.10 (0.83)</td>
<td></td>
</tr>
<tr>
<td>Wave 2 HcV, cm$^3$</td>
<td>6.18 (0.79)</td>
<td></td>
<td>6.87 (0.86)</td>
<td></td>
</tr>
<tr>
<td>Annual percent change in HcV</td>
<td>1.15 (1.06)</td>
<td></td>
<td>0.93 (1.17)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HcV, hippocampal volume; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; SD, standard deviation.

$^a$ Weight (kg)/height (m)$^2$.

$^b$ A higher score indicates better cognitive functioning.

Model 1 estimated the association between hippocampal atrophy and average of depressive symptoms over follow-up (wave 3–wave 5) adjusted for wave 2 CES-D scores. Among women with the same wave 2 scores, those with faster atrophy had significantly higher CES-D scores averaged over follow-up: A 2-standard-deviation increase in annual atrophy was associated with an average increase of 1.67 points (95% confidence interval (CI): 0.59, 2.77) in CES-D scores over the subsequent 6 years. HcV atrophy was not associated with depressive symptoms in men (coefficient = −0.05; 95% CI: −1.12, 1.03). Weighted models yielded similar results.

Model 2 assessed the association between HcV atrophy and changes in CES-D scores over follow-up (HcV atrophy*wave). As model 2 includes interactions, the coefficient for HcV atrophy estimates the association of atrophy with (concurrent) wave 2 CES-D scores, and the coefficients for subsequent study waves estimate the mean change in CES-D scores from wave 2 to the corresponding wave among subjects with no
Table 2. Distribution of Repeated Measures of Depressive Symptoms and Changes in Symptoms Over the Course of Follow-up in the Analytic Sample, Three-City Dijon MRI Study, Dijon, France, 1999–2011

<table>
<thead>
<tr>
<th>Study Wave (Years)</th>
<th>Women</th>
<th>Men</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean Change (SD)</td>
<td>No.</td>
<td>Mean (SD)</td>
<td>Mean Change (SD)</td>
<td>No.</td>
</tr>
<tr>
<td>Wave 2 (2003–2005)</td>
<td>10.76 (8.54)</td>
<td>814</td>
<td>6.07 (5.68)</td>
<td>495</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wave 4 (2007–2009)</td>
<td>10.34 (9.37)</td>
<td>−0.97 (8.24)</td>
<td>575</td>
<td>6.64 (6.63)</td>
<td>−0.33 (5.93)</td>
<td>351</td>
</tr>
<tr>
<td>Wave 5 (2009–2011)</td>
<td>9.85 (7.13)</td>
<td>0.42 (7.32)</td>
<td>459</td>
<td>7.19 (6.13)</td>
<td>0.91 (5.18)</td>
<td>273</td>
</tr>
</tbody>
</table>

Abbreviations: MRI, magnetic resonance imaging; SD, standard deviation.

* Measured using the Center for Epidemiologic Studies-Depression scale. Higher scores indicate more depressive symptoms.

b Mean change corresponds to the change between subsequent study visits computed for subjects who have both scores being compared. Positive changes indicate worsening of symptoms. Scores increased on average from wave 2 to wave 3 and from wave 4 to wave 5 but decreased from wave 3 to wave 4.

Table 3. Hippocampal Atrophy and Subsequent Depressive Symptoms in the Analytic Sample, Three-City Dijon MRI Study, Dijon, France, 1999–2011

<table>
<thead>
<tr>
<th>Hippocampal Atrophy</th>
<th>Women</th>
<th>Men</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unweighted Analysis</td>
<td>Weighted Analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>β</td>
<td>95% CI</td>
<td>β</td>
<td>95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HcV atrophy</td>
<td>1.67</td>
<td>0.59, 2.77</td>
<td>1.40</td>
<td>0.23, 2.57</td>
<td>−0.05</td>
<td>−1.12, 1.03</td>
</tr>
<tr>
<td>Wave 3i</td>
<td>0.40</td>
<td>−0.58, 1.38</td>
<td>0.53</td>
<td>−0.45, 1.52</td>
<td>1.63</td>
<td>0.85, 2.40</td>
</tr>
<tr>
<td>Wave 4i</td>
<td>0.26</td>
<td>−0.76, 1.29</td>
<td>0.58</td>
<td>−0.48, 1.64</td>
<td>1.32</td>
<td>0.52, 2.12</td>
</tr>
<tr>
<td>Wave 5i</td>
<td>0.06</td>
<td>−1.01, 1.13</td>
<td>0.35</td>
<td>−0.81, 1.50</td>
<td>1.53</td>
<td>0.58, 2.49</td>
</tr>
<tr>
<td>HcV atrophy*wave 3j</td>
<td>1.97</td>
<td>0.68, 3.24</td>
<td>1.82</td>
<td>0.53, 3.12</td>
<td>0.14</td>
<td>−1.04, 1.31</td>
</tr>
<tr>
<td>HcV atrophy*wave 4l</td>
<td>0.02</td>
<td>−1.40, 1.44</td>
<td>−0.68</td>
<td>−2.20, 0.85</td>
<td>−0.75</td>
<td>−2.08, 0.56</td>
</tr>
<tr>
<td>HcV atrophy*wave 5l</td>
<td>0.63</td>
<td>−0.97, 2.22</td>
<td>0.15</td>
<td>−1.67, 1.95</td>
<td>0.61</td>
<td>−1.26, 2.48</td>
</tr>
</tbody>
</table>

Abbreviations: CES-D, Center for Epidemiologic Studies-Depression scale; CI, confidence interval; HcV, hippocampal volume; MRI, magnetic resonance imaging.

a HcV atrophy is the independent variable expressed as a 2-standard-deviation increase in the annualized percent atrophy between baseline HcV and wave 2 HcV.
b The outcomes are depressive symptoms repeatedly measured over follow-up using the CES-D (score range, 0–60); higher scores indicate more depressive symptoms.
c Inverse probability-weighted linear mixed models.
d β coefficient for HcV atrophy in model 1 estimates the change in CES-D scores averaged over follow-up (wave 3–wave 5) for a 2-standard-deviation increase in HcV atrophy, with adjustment for 1) baseline values of educational level, total intracranial volume, diabetes, cognitive functioning, history of cardiovascular or cerebrovascular conditions, hypertension, alcohol consumption, body mass index, and smoking status; 2) time-varying indicator of place of study visit; 3) CES-D scores at wave 2; and 4) binary indicators of study wave.
e P < 0.01.
f P < 0.05.
g Linear mixed model 2 estimates the association between HcV atrophy and change in CES-D scores over follow-up; this model includes HcV atrophy, binary indicators for study wave, interaction terms between HcV atrophy, and indicators of study wave and was adjusted for 1) baseline values of educational level, total intracranial volume, diabetes, cognitive functioning, history of cardiovascular or cerebrovascular conditions, hypertension, alcohol consumption, body mass index, and smoking status and 2) time-varying indicator of place of study visit.
h β coefficient of HcV atrophy in model 2 estimates the change in concurrent wave 2 CES-D scores for a 2-standard-deviation increase in HcV atrophy.
i β coefficients of binary indicators of study wave estimate the mean change in CES-D scores from wave 2 to the corresponding follow-up wave among subjects with no atrophy.
j β coefficients for the interaction terms estimate the additional change in CES-D scores from wave 2 to the corresponding follow-up wave for a 2-standard-deviation increase in HcV atrophy.

atrophy. Finally, the atrophy\*wave coefficients estimate by how much the change in CES-D from wave 2 to the corresponding wave increases for each 2-standard-deviation increase in atrophy rates. In women, each 2-standard-deviation increase in atrophy was associated with a 1.17-point (95% CI: −0.08, 2.42; \( P = 0.07 \)) increase in concurrent wave 2 CES-D scores. Faster atrophy was associated with significant increases in scores in the subsequent 2 years after atrophy was measured (atrophy\*wave 3 coefficient); for every 2-standard-deviation increase in the rate of annual HcV atrophy, CES-D scores increased from wave 2 to wave 3 by an additional 1.97 points (95% CI: 0.68, 3.24; \( P = 0.003 \)) relative to the nonsignificant 0.4-point increase in scores among women with no atrophy (95% CI: −0.58, 1.38).

Atrophy\*wave 4 and atrophy\*wave 5 coefficients were nonsignificant, indicating that longer-term changes in symptoms (from wave 2 to wave 4 or wave 5) were not related to HcV atrophy in women. HcV atrophy was not associated with wave 2 CES-D scores or changes in CES-D scores in men. Results from IPWs analyses were similar.

Figure 2 compares changes over follow-up in mean values of CES-D scores, estimated from the model 2, between subjects in the highest quartile of hippocampal atrophy and those in the 3 lower quartiles. Women with faster atrophy had CES-D scores that were 2 to 4 points higher across follow-up and showed greater increases in symptoms at 2 years after the atrophy. In men, trajectories were not different across levels of HcV atrophy.

We conducted sensitivity analyses by adjusting for 1) time-varying values of cognitive functioning, hypertension, and diabetes, 2) self-reported history of depression, or 3) additional covariates (baseline HcV, hypercholesterolemia, Apolipoprotein E-epsilon4 genotype, antidepressant use, white matter lesion progression, and physical functioning), but these adjustments did not alter the results. To account for depressive symptoms that were concomitant to the HcV atrophy in sensitivity analyses, we excluded subjects who had elevated depressive symptoms (above-threshold cut offs validated in the French population (27)) or reported antidepressant use before wave 2, and the conclusions remained unchanged.

**Additional analyses**

We re-ran models 1 and 2 using HcV at wave 2 as the predictor variable (Web Table 2). Women with larger HcV had lower CES-D scores averaged over follow-up; the association was statistically marginally nonsignificant (\( \beta = −0.67; 95\% \text{ CI}: −1.47, 0.13 \)). In women, larger HcV at wave 2 was associated with significantly lower concurrent CES-D scores (a 1-point decrease in scores per 1-cm\(^3\) increase in HcV; 95% CI: −2.12, −0.25) and with a marginally nonsignificant decrease in scores 2 years later (\( \beta = −0.68; 95\% \text{ CI}: −1.45, 0.09 \)). No associations between HcV and subsequent depressive symptoms were detected in men. Results were similar in sensitivity analyses of the association between baseline HcV and the 5 subsequent assessments of depressive symptoms.

**DISCUSSION**

In the present population-based cohort of older adults, we found that faster hippocampal atrophy was associated with more subsequent depressive symptoms in women but not in men. In addition, faster hippocampal atrophy was related to increases in symptoms over the subsequent 2 years but not with later changes in symptoms, suggesting a short-term association of atrophy with worsening of depressive symptoms in women. These results were unchanged in sensitivity analyses that accounted for 1) selective survival and attrition and 2) various relevant covariates, including cognitive functioning and history of previous depression.

To our knowledge, this is the first report on a relationship between HcV changes and subsequent depressive symptoms. Our findings are in agreement with prior research that provided indirect support to the hypothesis that HcV atrophy contributes to the manifestation of depression. Earlier support for this hypothesis came from studies in patients experiencing their first episodes of depression that found that reduced HcV was already present at early manifestation of symptoms (8, 9, 45). Recent findings in healthy subjects at high risk of depression also suggested that HcV could contribute to the risk of depression (10, 11). Chen et al. (11) reported reduced HcV in healthy young girls with a familial risk of depression. Baaré et al. (10) found that healthy...
twins who had a co-twin who had been diagnosed with depression had smaller HcV than did twins with no risk for depression. Similar results have been found for healthy relatives of patients with other psychiatric disorders, such as schizophrenia (46) and post-traumatic stress disorder (47). Together, these results indicate that HcV is a possible susceptibility factor for behavioral and psychological outcomes.

Another population-based study (16) found no association between baseline HcV and risk of high depressive symptomatology in older adults. That study had a smaller sample ($n = 514$), did not report sex-stratified results, and only examined the association of HcV (not changes in HcV) with depressive symptoms. Likewise, our results showed that HcV was not associated with subsequent depressive symptoms. However, we noted that these associations were close to statistical significance in women and were concordant with those observed for hippocampal atrophy (i.e., larger HcV was associated with fewer depressive symptoms). Our findings highlight the value of studying changes in HcV to examine subsequent mood outcomes. Indeed, measures of change can be more informative because they can differentiate between a pre-existing small volume and individual patterns of change in volume (stable vs. accelerated).

We found associations between hippocampal atrophy and subsequent depressive symptoms in women but not in men. Interestingly, studies in patients experiencing their first episodes of depression have only found smaller HcV in men (8, 9, 45). These studies were based on smaller ($n < 100$) and younger (age range, 18–64 years) samples, with one having an adolescent sample (age range, 13–18) (9), and therefore their study populations could be inherently different than ours. For instance, in our sample of subjects who were 65–80 years of age, HcV was not different in men and women, but hippocampal atrophy was faster in women. However, results on sex-related differences in HcV changes in adults are equivocal, and the discrepancy in results has been suggested to be a result of the inclusion of pre- and postmenopausal women in the same study (48). Indeed, one proposed explanation for these age- and sex-related differences in HcV is the protective role of estrogen in neural mechanisms (49, 50). Female sex hormones were shown to play a role in neurogenesis and neuroprotective mechanisms in the hippocampus (51, 52). In contrast, estrogen depletion and hormonal profiles in postmenopausal women have been linked to depression, poorer response to treatment, and deregulation of neural circuits highly present in the HcV and involved in depression, such as serotonergic pathways (49, 53). Together, these observations identify older women as a priority population for the study of HcV and mood changes. We note that our results in older adults, similar to those in younger patients experiencing their first episodes of depression (8, 9, 45), support the hypothesis that hippocampal atrophy can contribute to depression. However, the discrepancies in the findings by sex observed in our sample and these studies (8, 9, 45) suggest that the association between HcV and depression could have different nuances or characteristics in different age categories. Future studies on the longitudinal relationships between hippocampal atrophy and depressive symptoms in different age groups can help identify the age- and sex-related particularities of this relationship.

Although the population-based longitudinal design was necessary to address our research question, it also introduced conceptual and methodological challenges. A major concern is potential selection bias resulting from selective attrition and survival. We attempted to reduce these limitations by carefully examining predictors of attrition and adjusting for them in mixed models and using IPWs. However, these analyses assumed that outcomes were missing at random given the observed covariates, which cannot be verified. Our data and previous research suggest that censoring is related to having a worse-off profile (38, 40) (i.e., higher depressive symptoms, faster atrophy, and faster cognitive decline); this would result in a healthier sample and thus is more likely to attenuate our results than to produce biased estimates. Another challenge in studies of older adults is selective survival (related to exposure and outcome) up to enrollment in the study, which leads to a study population that is already healthier and differentially selected. Because we observed an association between hippocampal atrophy and depressive symptoms in these potentially healthier respondents after adjustment for multiple potential confounders and observed predictors of attrition, we do not suspect that the internal validity is jeopardized; however, the external validity might be limited, although some authors argue that representativeness is not a major limitation for association studies (54). Finally, because little is known about the mechanisms of the relationship between hippocampal atrophy and subsequent depressive symptoms, the generalizability of the findings beyond the age group of our sample may be limited, as discussed above.

Another potential weakness concerns the measurement of depressive disorders. The CES-D score measures depressive symptoms over a 1-week period and thus does not differentiate between transient and chronic symptoms or produce a clinical diagnosis. To assess severity of symptoms, we used generalized estimation equations models and a categorical classification of elevated (above-threshold) symptoms (27). These results were concordant with those obtained with continuous CES-D scores: In women, a 2-standard-deviation (2.12%) faster rate of atrophy was associated with a 1.42 times higher risk of reporting elevated depressive symptoms over follow-up (95% CI: 1.08, 1.88). In contrast, HcV (measured at wave 2) was not linked to elevated symptoms (relative risk = 0.92; 95% CI: 0.74, 1.15). In addition to increasing power, using the continuous CES-D scale in this context is more informative; it allowed us to look at both average depressive symptoms and worsening of symptoms over follow-up.

In conclusion, we examined the relationship between hippocampal atrophy and future depressive symptoms using a population-based prospective cohort of older adults, repeated measures of HcV and depressive symptoms, and methods that accounted for longitudinal data and selective attrition and found that faster hippocampal atrophy was associated with more subsequent depressive symptoms and with early, but not late, changes in symptoms in women but not in men. To our knowledge, our study is the first to explore temporal relationships between hippocampal atrophy and subsequent depressive symptoms. The results, in combination with prior research, emphasize the role of hippocampal changes in the manifestation of mental health conditions, mainly mood symptoms in older women.
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