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1 Title:

2 Presymptomatic atrophy in autosomal dominant Alzheimer's disease: a serial MRI  
3 study

4

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1 Abstract

2 INTRODUCTION: Identifying at what point atrophy rates first change in Alzheimer's  
3 disease is important for informing design of presymptomatic trials.

4 METHODS: Serial T1-weighted MRI scans of 94 participants (28 non-carriers, 66  
5 carriers) from the Dominantly Inherited Alzheimer Network (DIAN) were used to  
6 measure brain, ventricular and hippocampal atrophy rates. For each structure, non-  
7 linear mixed effects models estimated the change-points when atrophy rates deviate  
8 from normal and the rates of change before and after this point.

9 RESULTS: Atrophy increased after the change-point, which occurred 1-1.5 years  
10 (assuming a single step change in atrophy rate) or 3-8 years (assuming gradual  
11 acceleration of atrophy) before expected symptom onset. At expected symptom  
12 onset, estimated atrophy rates were at least 3.6 times those before the change-point.

13 DISCUSSION: Atrophy rates are pathologically increased up to seven years before  
14 "expected onset". During this period, atrophy rates may be useful for inclusion and  
15 tracking of disease progression.

16

17

18 Keywords: Longitudinal, Atrophy, Alzheimer's disease, Dementia, Autosomal  
19 dominant, Neuroimaging, MRI, Boundary Shift Integral, Non-linear modeling,  
20 Change-point

## 1 1. Background

2 Testing potentially disease-modifying treatments for Alzheimer's disease (AD) during  
3 the preclinical phase [1] presents challenges of recruitment and staging of  
4 asymptomatic individuals, as well as determining suitable measures for assessing  
5 disease modification. One recruitment strategy is to study members of families  
6 known to carry a pathogenic mutation in a gene – *presenilin 1 (PSEN1)*, *presenilin 2*  
7 (*PSEN2*) or *amyloid precursor protein (APP)* – that causes autosomal dominant AD  
8 (ADAD). These mutations have almost 100% penetrance and ~50% of at-risk  
9 individuals are carriers. ADAD typically has an early and relatively predictable age at  
10 symptom onset [2,3]. The Dominantly Inherited Alzheimer Network (DIAN) is a  
11 multicentre observational study of individuals at risk of, or affected by, ADAD. DIAN  
12 performs longitudinal assessments of imaging, fluid biomarkers, and cognitive  
13 function, which reflect pathological features in ADAD [4] and sporadic AD [5]. In  
14 particular, cerebral atrophy measures derived from volumetric magnetic resonance  
15 imaging (MRI) are used as biomarkers of neurodegeneration and as outcome  
16 measures in trials [6].

17

18 Longitudinal data from presymptomatic ADAD individuals provide a unique  
19 opportunity to determine when atrophy rates begin to diverge from normal. Previous  
20 cross-sectional, or small longitudinal studies report a wide range of estimates of this  
21 point of divergence: from 10 years before [4,7] to 7 years after [8] expected clinical  
22 onset (as determined by the affected parent's age at onset).

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Abbreviations: DIAN = Dominantly Inherited Alzheimer Network; ADAD = autosomal dominantly inherited familial AD; PSEN1 = presenilin 1; PSEN2 = presenilin 2; APP = amyloid precursor protein; EAO = expected age at onset; EYO = estimated years to expected symptom onset; NC = mutation non-carriers; pMut+ = presymptomatic mutation carriers; qMut+ = questionably or mildly symptomatic mutation carriers; sMut+ = overtly symptomatic mutation carriers.

1  
2 We used serial MRI data from DIAN to model cerebral atrophy rates during  
3 presymptomatic and early symptomatic stages of ADAD. We assessed whole brain  
4 and hippocampal atrophy and ventricular expansion, three well-established imaging  
5 measures used as exploratory endpoints in clinical trials [6]. We hypothesize that  
6 presymptomatic carriers have similar atrophy rates to non-carriers up until a 'change-  
7 point' when the biomarker starts to diverge from normal. This hypothesis is  
8 consistent with models of sporadic AD [5] that assume a sigmoidal trajectory, and  
9 cross-sectional findings from the DIAN cohort [4,7]. We used two non-linear mixed  
10 effects models (Supplementary Appendix A) to estimate the timing of change-points  
11 relative to expected symptom onset, and atrophy rates before and after these  
12 change-points. The first model assumes that the atrophy rate undergoes a single  
13 'step change' to a new, stable value; whereas the second model assumes a 'gradual  
14 acceleration' in atrophy rate after the change-point. These models help characterize  
15 when therapeutic effects on brain atrophy could potentially be observed in  
16 presymptomatic ADAD and could help focus future sample size calculations for  
17 upcoming prevention trials.

18

## 19 2. Methods

### 20 2.1 Participants and Procedures

21 All participants were members of DIAN [9], and details of participating sites are  
22 available (<http://dian-info.org/>). The study received prior approval from appropriate  
23 Institutional Review Boards and Ethics Committees at each site. Informed consent  
24 was obtained from all participants.

25

1 Genotyping was performed to determine the presence of an ADAD mutation for each  
2 at-risk participant. A semi-structured interview assessed the expected age at onset  
3 (EAO), based on when the affected parent first showed progressive cognitive  
4 decline. Expected years to symptom onset (EYO) is the difference between age at  
5 scan and EAO [3]. Negative values indicate years before expected onset and  
6 positive values years after.

7  
8 At the sixth data freeze (July 2013), there were 102 participants with two or more  
9 MRI scans available and complete data (mutation status, age, EAO, and global  
10 Clinical Dementia Rating (CDR) score [10]).

## 11 12 2.2 Volumetric MRI

13 Volumetric T1-weighted scans were acquired on 3 Tesla MRI scanners using  
14 Alzheimer's Disease Neuroimaging Initiative (ADNI) standardized protocols [11] and  
15 corrected for intensity inhomogeneity [12]. Whole brain and hippocampal regions  
16 were automatically segmented [13–15]. Lateral ventricles were delineated semi-  
17 automatically by an expert rater. Baseline volumetric measures were corrected for  
18 total intracranial volume (TIV), calculated using an automated technique [16]. For  
19 each structure, volume change was directly measured using a group-wise  
20 implementation [17–19] of the Boundary Shift Integral (BSI) [20] to ensure  
21 longitudinal consistency. A trained image analyst, blinded to participants' mutation  
22 and clinical status, reviewed all raw and processed images.

## 23 24 2.3 Clinical Classification

1 Participants were classified into four groups, based on mutation status, global CDR  
2 score, and actual age at onset (where this had occurred), determined by Uniform  
3 Data Set form B9, “Clinical Judgment of symptoms” [21]:

4

5 • **Mutation non-carriers (NC)**; our control group.

6 • **Presymptomatic mutation carriers (pMut+)**; included mutation carriers with  
7 a global CDR score of 0 at both their first two visits.

8 • **Questionably or mildly symptomatic mutation carriers (qMut+)**; included  
9 participants with at least one global CDR score of 0.5 during their first two  
10 visits, with the other visit being either 0 or 0.5. We excluded from this group  
11 participants who had a reported onset more than four years before study  
12 entry.

13 • **Overtly symptomatic mutation carriers (sMut+)**; included participants with  
14 a CDR score of 1.0 or greater at either (or both) of their first two visits or who  
15 were more than four years after reported onset at study entry.

16

17 Eight participants were excluded from the analysis: seven (one NC, four pMut+, one  
18 qMut+, one sMut+) were identified during initial visual review of the image data and  
19 excluded due to non-Alzheimer’s pathology (e.g. infarct, neoplasm), imaging  
20 artifacts, or acquisition-related changes likely to result in unreliable atrophy  
21 measures. An additional participant (qMut+) was excluded due to moderate motion  
22 artefact on follow-up imaging and implausible growth in brain and hippocampi. As  
23 part of the sensitivity analysis, we re-ran the model including this participant  
24 (Supplementary Appendix B).

25



1 Two participants who initially satisfied the qMut+ criteria were retrospectively re-  
2 classified as sMut+, as both participants had consistent evidence of cognitive decline  
3 over a sustained period.

4  
5 Our final sample therefore included 94 participants: 24 pMut+, 18 qMut+, 24 sMut+,  
6 and 28 NC. Of the 66 carriers, 54 had mutations in PSEN1, three in PSEN2, and  
7 nine in APP. There were 66 participants with two MR scans, 20 with three, and eight  
8 with four scans. The scan interval between baseline to follow-up ranged from 0.9 to  
9 3.3 years, and was independent of carrier status or clinical severity. Two participants  
10 (one qMut+ and one sMut+) had inadequate image quality for analyses involving  
11 hippocampi.

12

#### 13 2.4 Statistical analysis

14 To compare baseline values between each of the three mutations groups (pMut+,  
15 qMut+, sMut+) and the non-carrier group, ANOVA models were used for age, EYO,  
16 and TIV, while logistic regression was used for APOE  $\epsilon$ 4 positivity and sex. A  
17 generalized least squares linear regression model that allows different group-specific  
18 residual variances was used to compare baseline volumes (standardized to mean  
19 TIV) between each of the three carrier groups and non-carriers.

20

21 The change-point model [22–24] was used to explore brain, ventricular and  
22 hippocampal atrophy rates (Supplementary Appendix A provides a detailed model  
23 description). As the focus of our study was the presymptomatic and earliest  
24 symptomatic stages of ADAD, the model included non-carriers (NC),  
25 presymptomatic, and questionably symptomatic carriers (pMut+/qMut+).

1

2 Figure 1 provides a schematic representation of the ‘step change’ and ‘gradual  
3 acceleration’ change-point models. In both,  $\beta$  represents the shared atrophy rate for  
4 NC and pMut+/qMut+ groups before the change-point, which takes place  $\delta$  years  
5 before or after the EAO. Due to limited data,  $\delta$  (for a specific brain structure) was  
6 assumed to be the same for all pMut+/qMut+ individuals.

7

8 For the ‘step change’ model,  $\gamma$  is the change in atrophy rate for the pMut+/qMut+  
9 group after the change-point. In the ‘gradual acceleration’ model, the atrophy rate for  
10 the pMut+/qMut+ group accelerates after the change-point by a value of  $2\gamma$  per year.  
11 With each model, we estimated  $\beta$ ,  $\gamma$  and  $\delta$  for each region, and using these we  
12 estimated atrophy rates at various points before and after EAO.

13

14 Our change-point model was not designed to estimate atrophy rates several years  
15 after symptom onset; to do so risked distorting a model that was designed to focus  
16 on the progression from early changes to clinical symptoms. Thus, a separate linear  
17 mixed-effects random-slopes model (with no change-point) was used to model  
18 atrophy rates of the sMut+ group, assuming all observations were after the change-  
19 point.

20

21 The change-point models are non-linear extensions of a previously described linear  
22 mixed-effects random-slopes model [25] (Supplementary Appendix A). Atrophy  
23 measures were log-transformed to provide symmetric approximations of percentage  
24 change from baseline. The change-point models were implemented using SAS

1 (version 9.4) procedure NLMIXED, which simultaneously estimated  $\beta$ ,  $\gamma$  and  $\delta$ .  
2 Robust estimates of uncertainty for these coefficients were obtained through  
3 bootstrapping [26,27], with 10,000 replicates and using bias corrected and  
4 accelerated (BCa) 95% confidence intervals. Sensitivity of the estimates and  
5 confidence intervals to outliers was explored (see Supplementary Appendix B).

6

### 7 3. Results

8 Table 1 summarizes demographic and clinical data. The sMut+ group was, as  
9 expected, older than the non-carriers, with smaller brain and hippocampal volumes,  
10 and larger ventricular volumes (all TIV-adjusted), reflecting pathological losses and  
11 larger TIV, which likely reflects the higher (albeit statistically non-significant)  
12 proportion of males in this group. The qMut+ group had smaller hippocampal  
13 volumes and larger ventricular volumes compared to non-carriers, while the preMut+  
14 group just had smaller right hippocampal volumes.

15

16 Table 2 shows the change-point model results for each structure. In the 'step  
17 change' model, the pre-change atrophy rate ( $\beta$ ) was statistically significant in every  
18 structure except the right hippocampus. In all regions, there were significant  
19 increases in atrophy rate ( $\gamma$ ) after the change-point. This is demonstrated by  
20 deriving, from the results of the model, a ratio between the atrophy rate at EAO (1-0  
21 years before) to the pre-change atrophy rate. This ratio was 4.0 for whole brain, 4.5  
22 for ventricles, and 9.0 for left hippocampus, but it could not be produced for right  
23 hippocampus as the estimated pre-change atrophy rate was small and not  
24 statistically significantly different from zero. However, the increase in atrophy rate ( $\gamma$ )  
25 after the change-point for the right hippocampus was larger than the corresponding

1 coefficient in the results for the left hippocampus. The estimated change-point ( $\delta$ ) for  
2 brain, ventricle and left hippocampus was 1.4 years before EAO and 1.1 years  
3 before EAO for the right hippocampus. For whole brain and left hippocampus, the  
4 confidence intervals for  $\delta$  did not span zero, providing evidence that they occurred  
5 before EAO. Estimates of the ventricular change-point had greater uncertainty (-1.1  
6 to 13.5 years) than the other structures. Table 2 provides estimates for rates of  
7 change at various times before and after EAO.

8  
9 As with the 'step change' model, in the 'gradual acceleration' model all structures  
10 except the right hippocampus had statistically significant pre-change atrophy rates.  
11 All regions had coefficients ( $\gamma$ ) indicating statistically significant increased  
12 neurodegeneration after the change-point. The ratio of atrophy rate at EAO to the  
13 pre-change rate was 3.6 for whole brain, 4.1 for ventricles, and 5.1 for left  
14 hippocampus. The ratio for the right hippocampus was also not available due to the  
15 small, non-significant pre-change atrophy rate, but the coefficient ( $\gamma$ ) indicated that  
16 the right hippocampus had a similar increase towards neurodegeneration as the left.  
17 The change-point estimates ( $\delta$ ) for the whole brain and ventricles were 3.0-4.6 years  
18 earlier than for the hippocampi. For all structures, the confidence intervals for  $\delta$  did  
19 not span zero. Figure 2 shows estimated atrophy rates and 95% confidence intervals  
20 from both models in relation to EYO.

21  
22 In the sensitivity analysis, we re-ran the model including the participant with  
23 movement artefact and clinically implausible data (Supplementary Appendix B). The  
24 pattern of the results was not materially altered although the statistical significance of  
25 some parameter estimates was lost.

1

2 The estimated rates of change in sMut+ participants were approximately double  
3 those found in pMut+/qMut+ carriers at EAO using the change-point models. The  
4 symptomatic rates were: -2.41% (95% CI: -2.88, -1.95) per year for whole brain,  
5 15.0% (95% CI: 12.6,17.5) for ventricles, -4.70% (95% CI: -6.39, -3.01) for left  
6 hippocampus, and -4.64% (95% CI: -5.68, -3.60) for right hippocampus.

7

#### 8 4. Discussion

9 The goal of this study was to estimate when brain, ventricular and hippocampal  
10 volume changes in ADAD diverge from non-carriers, and to model the rates before  
11 and after this transition using serial MRI data from the DIAN cohort. We designed  
12 two non-linear mixed effects models: one assuming a single 'step-change' and  
13 another assuming a 'gradual acceleration' in rates of atrophy after the change-point.  
14 This type of model has previously been used to investigate the trajectories of  
15 cognitive decline [23,28] and atrophy rates [29,30]. In all cases, there was evidence  
16 of increased atrophy after the change-point, suggesting that our models better reflect  
17 the non-linear nature of atrophy in early-stage disease than a linear relationship  
18 would. The 'gradual acceleration' model found evidence for all assessed regions that  
19 atrophy rates diverge from normal values before symptom onset, with the change-  
20 point occurring 3.0 to 7.6 years before EAO. The 'step change' model found a  
21 change-point of 1.4 years before EAO for whole brain and left hippocampus but was  
22 unable to show evidence of a change-point preceding EAO for ventricles or right  
23 hippocampus.

24

#### 25 4.1 Interpreting the change-point model results

1 A key advantage of using two different change-point models is that they provide  
2 complementary information about the timing of the change-point. The 'step change'  
3 model provides the most conservative estimate of when atrophy rates diverge. In  
4 contrast, the 'gradual acceleration' model is probably more biologically plausible,  
5 based on previous results in ADAD [4,7,31,32] and by the well-characterised spatial  
6 spread of neurodegeneration [33] that typically begins in the medial temporal lobe  
7 and gradually spreads into neocortical regions. However, there are caveats to the  
8 gradual acceleration model used. The non-linear nature of the atrophy may vary  
9 between individuals and a quadratic may not be the most appropriate fit. However,  
10 given the size of the dataset, this approach minimizes risk of overfittings. Change-  
11 point models also avoid some of the pitfalls that can occur when including polynomial  
12 terms in a linear regression to model this non-linear relationship [34]. While a  
13 quadratic term could better capture the increase in atrophy rate observed around  
14 expected onset, it may also produce artefacts of increased atrophy in carriers who  
15 are decades before their expected onset.

16

17 Unlike linear models, change-point models can capture the different phases of  
18 atrophy/expansion during the long period of presymptomatic disease progression.  
19 Both models provide similar estimates of  $\beta$  (see Table 2), the pre-change atrophy  
20 rate. This suggested age-related changes broadly consistent with previous aging  
21 studies [35–37] showing small but significant rates of whole-brain atrophy of the  
22 order of 0.2-0.6%/year and hippocampal atrophy of the order of 0.3-0.4%/year for  
23 similar age ranges to this cohort. From both models, there was evidence of  
24 increased atrophy after the change-point in all regions.

25

## 1 4.2 Estimating onset of pathological atrophy

2 It is unclear when disease-related atrophy first becomes evident in ADAD. Cross-  
3 sectional results from *PSEN1* E280A mutation carriers [38,39] and DIAN [4,7]  
4 suggest atrophy of hippocampi diverge from non-carriers ~6 years and 10 years  
5 before symptom onset, respectively; earlier than in our models. However, initial  
6 longitudinal results from DIAN [7] (N=53) identified increased atrophy rates only in  
7 symptomatic carriers. A study of 13 presymptomatic *PSEN1* carriers found increased  
8 cortical thickness at baseline but subsequent thinning of a number of cortical regions  
9 [40], suggesting a non-linear nature to presymptomatic changes – with grey matter  
10 increases preceding declines.

11  
12 Most previous longitudinal volumetric MRI studies of ADAD mutation carriers have  
13 been relatively small, single-site studies. One study following presymptomatic  
14 participants to clinical onset indicated pathological hippocampal atrophy rates  
15 appeared ~5.5 years before AD diagnosis [31]. Weston et al. [41] examined cortical  
16 thickness longitudinally in presymptomatic carriers and detected significant losses in  
17 the precuneus eight years before EAO. These values are consistent with our findings  
18 using a gradual acceleration model where the change point was 7.6 years before  
19 onset. However, another study of 16 ADAD mutation carriers (seven with long-term  
20 follow-up) did not detect structural MRI changes until *after* symptom onset [8],  
21 suggesting that a heterogeneity in these small cohorts and the methods used to  
22 analyze them may generate markedly different results.

23  
24 No prior ADAD study has used change-point models, making it difficult to compare  
25 estimates. However, there are similarities between our findings and sporadic AD

1 studies that used similar approaches. A study of 79 elderly patients, 37 of whom  
2 developed mild cognitive impairment (MCI), reported a ventricular expansion  
3 change-point 2.3 years before MCI diagnosis [29]. Another longitudinal study  
4 (N=296, 66 progressing to MCI) found a similar hippocampal atrophy change-point of  
5 2-4 years before clinical onset [30]. Their estimate of a 0.2% per year pre-change  
6 hippocampal atrophy rate accords with ours (0.2% left, 0.1% right). Their post-  
7 change atrophy rate estimate for the right hippocampus (2.7%/year) was similar to  
8 our value (2.5%) whereas their left hippocampal rate estimate (1.2%) was lower than  
9 our (2.1%).

10

#### 11 4.3 Predicting clinical onset in ADAD

12 An important challenge is what estimate to use for clinical onset before it has  
13 occurred. Many studies, including ours, use an EAO based on when the affected  
14 parent first developed symptoms consistent with progressive decline. Other  
15 measures are based on the average across all previously affected family members,  
16 or the reported age at onset in the literature for a particular mutation [3]. However,  
17 each is an imperfect estimate of the future age at onset.

18

19 If future clinical trials use EYO as an inclusion criterion, then it is the distribution of  
20 atrophy rates relative to EAO that is of importance. However, if we wish to  
21 understand the etiology of the disease, then the distribution of atrophy rates relative  
22 to actual onset is more informative, as change-points are likely to be more strongly  
23 related to actual rather than expected age at onset. The effect of switching from  
24 actual to expected onset in statistical models will change the form of the estimated  
25 volume change over time, smoothing it to some degree. Without knowledge of actual



1 onset, this effect is not easily avoided. We did, however, attempt to reduce its impact  
2 by excluding overtly symptomatic carriers from our change-point models.

3

4 Identifying precisely when clinical onset has occurred is not straightforward. To  
5 facilitate standardization across sites, DIAN rigorously monitors how raters perform  
6 CDR and other assessments [42]. In at-risk individuals, other factors can influence  
7 cognitive function or behavioral changes, including stress, anxiety, and the constant  
8 level of vigilance and introspection that participants experience. In this study, there  
9 were six qMut+ participants who reverted from a baseline global CDR of 0.5 to 0 at  
10 follow-up. These cases highlight the subtle nature of transitions from unimpaired to  
11 “affected” and the potential confounds of mood disturbance and other factors. We  
12 addressed this uncertainty by including questionably or mildly symptomatic carriers  
13 in our change-point models.

14

#### 15 4.4 Limitations and future work

16 Change-point models have been used to model atrophy rates in preclinical sporadic  
17 AD [29,30]. We expand on these approaches by adapting the model for repeated  
18 measures of direct change instead of individual volumetric measures and allowing  
19 for either a ‘step change’ or ‘gradual acceleration’ after the change-point. Due to the  
20 non-linear nature of our models, and the use of bootstrapping to obtain confidence  
21 intervals for the model coefficients, these models are susceptible to influential  
22 outliers, especially with smaller sample sizes (see the sensitivity analysis in  
23 Supplementary Appendix B). Additional longitudinal data should provide improved  
24 robustness against such issues.

25

1 No prior study has characterized the progression of atrophy in such a large cohort of  
2 presymptomatic and earliest symptomatic ADAD. DIAN is currently recruiting  
3 participants into a multicentre clinical trial [43], and the samples from our analysis  
4 should more closely reflect a clinical trial setting. Whole brain, lateral ventricles, and  
5 hippocampi are the most studied structures in sporadic AD, and are often used as  
6 trial outcome measures. From the results, these atrophy measures appear to be  
7 elevated compared to non-carriers approximately 5 years before expected onset,  
8 making them best suited for prevention trials in ADAD from this period onward.  
9 Given the evidence of presymptomatic atrophy in specific cortical regions [40,41],  
10 future application of the change-point model could involve studying atrophy rates of  
11 specific cortical structures, such as the precuneus and posterior cingulate. Atrophy in  
12 these structures may appear earlier and thus be better suited for trials that target  
13 presymptomatic patients. In addition, the model should incorporate information from  
14 other biomarkers, including CSF amyloid and tau concentrations, to determine how  
15 markers of these pathologies affect the timing of the change-point. Finally, it is  
16 essential to understand which preclinical changes in ADAD generalize to sporadic  
17 AD, as differences in the structures preferentially affected appear to exist [44].

18

#### 19 4.5 Conclusions

20 Atrophy rates increase in ADAD some years before expected symptom onset. Using  
21 two different change-point models, we can characterize when this change occurs.  
22 The 'step-change' model provides a minimum estimate, 1.4 years before expected  
23 onset. The 'gradual acceleration' model provides a more biologically plausible  
24 approach towards how atrophy rates diverge from normal, with brain atrophy rates  
25 showing pathological acceleration ~7.6 years before expected onset and

- 1 hippocampal rates changing ~3.0 years before expected onset. These models may
- 2 help predict the time to clinical onset for presymptomatic individuals with increased
- 3 atrophy and identify individuals for prevention trials.

1 Figure captions

2

3 **Figure 1: Schematic representation of the ‘step change’ (Figure 1a) and**  
4 **‘gradual acceleration’ (Figure 1b) change-point models.**

5

6 **Figure 2: Rates of change estimated from the ‘step change’ and ‘gradual**  
7 **acceleration’ models, as a function of the estimated years from symptom**  
8 **onset (EYO) for the pMut+/qMut+ carriers.**

9 The figure shows the relationship between rate of annualized volume change (%)  
10 and EYO. 95% confidence intervals are included, computed from the bootstrap  
11 samples. While the schematics in Figure 1 display the decline in actual volume,  
12 these graphs represent the rate of change in volume. A horizontal line indicates the  
13 estimated atrophy rate (from the ‘step change’ model) for non-carriers and carriers  
14 before the change-point before any deviation from normal rates of change. Vertical  
15 dotted lines indicate the change-points for both the ‘step change’ and ‘gradual  
16 acceleration’ models. For periods that include the change-point, the estimated rate of  
17 atrophy is a weighted combination representing the transition from the pre-change-  
18 point atrophy to the post-change-point atrophy. Top left: whole brain; top right: lateral  
19 ventricles; bottom left: left hippocampus; bottom right: right hippocampus.

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