WHITE MATTER HYPERINTENSITY INCREASES ARE A FEATURE OF FAMILIAL ALZHEIMER'S DISEASE AND ARE ASSOCIATED WITH INCREASED BRAIN ATROPHY

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Introduction:

White matter hyperintensities (WMH) are areas of hyperintense signal on T2/FLAIR MRI imaging and are associated with deterioration in a number of cognitive domains in later life. They are increasingly recognised in the aetiology of late-onset (sporadic) Alzheimer's disease and are widely thought to be a result of vascular disease. Less is known about WMH in individuals with autosomal dominant familial AD, a younger group in whom comorbidities are rarer.

Aims:

1. **To assess how WMH change over time differs between controls and *PSEN1*, *PSEN2* and *APP* mutation groups.**
2. **To assess whether WMH burden increases as estimated onset is approached and passed.**
3. **To assess whether WMH changes and brain atrophy rates are associated markers across the disease course.**

❖ Model 1: Mixed-effect linear regression: assessing WMH accrual in each mutation group

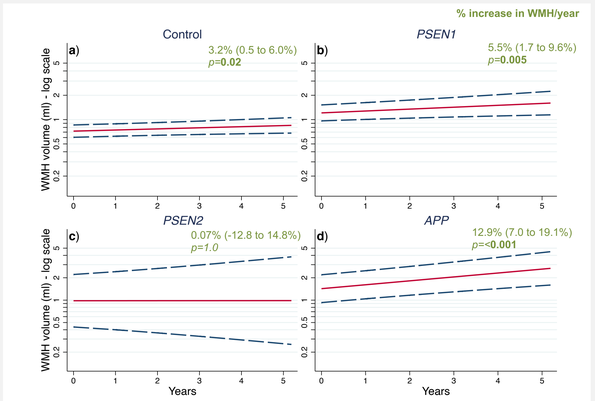


Figure 2: WMH change over time from baseline by mutation group
Plots show mean WMH change over time from baseline on a log scale in each mutation group, with 95% confidence intervals and standardised to mean TIV. Estimates for percentage increases in WMH volume (ml) per year with 95% confidence intervals and *p* values, calculated from separate linear mixed-effect regression models, are shown in green.

❖ Model 2: Mixed-effect linear regression: exploring the role of mutation group and cognitive impairment

	Controls (Slopes/*intercepts*)	*PSEN1* (Slopes/*intercepts*)	*PSEN2* (Slopes/*intercepts*)
PSEN1	0.2 / *0.6*		
PSEN2	0.8 / *0.6*	0.7 / *0.4*	
APP	**0.002** / ***0.03***	**<0.001** / ***0.02***	0.1 / *0.2*
Overall difference	**0.008** / *0.05*		

Table 2: Between-group differences in WMH change over time from baseline, and baseline volume
The table shows *p* values for mutation group differences in slope and intercept, from a model that allows for a mutation group / symptom status interaction and is standardised to mean TIV.

- There was a significant increase in WMH over time in control, *PSEN1* and *APP* groups, with the greatest increase of 12.9% per year observed in the *APP* group.
- There was a significant difference in rates of WMH accrual over groups, with the highest rate in the APP group, allowing for the effect of symptom group.

Methods - Cohort

❖ 201 individuals from the Dominantly Inherited Alzheimer network (DIAN)

	Control	*PSEN1*	*PSEN2*	*APP*	*p* value across groups
N (total=201)	72	95	7	27	
Age	38.9 (10.5)	40.0 (10.6)	42.3 (12.6)	42.9 (9.8)	0.4
Male (%)	63	61	43	63	0.8
APOE-ε4 positive (%)	25	26	43	26	0.7
Estimated years from expected symptom onset	-7.1 (10.7)	-4.5 (9.6)	-7.5 (13.6)	-5.5 (9.4)	0.4
Symptom status; n(%):					
Presymptomatic	-	41 (43%)	5 (71%)	15 (54%)	**<0.001**
Questionably symptomatic	-	34 (36%)		8 (30%)	
Symptomatic	-	20 (22%)		4 (14%)	
Length of follow up; min, max (years)	2.8 (0.8); 1.9, 5.0	2.6 (1.1); 0.9, 5.2	3.6 (0.5); 3.0; 4.3	2.6 (1.3); 1.0, 5.1	**0.008**
TIV (ml)	1387 (132)	1378 (136)	1497 (139)	1418 (166)	0.1
Log_eWMH (ml) [a]	0.7 (2.2)	1.2 (3.2)	1.4 (2.6)	1.5 (3.1)	0.3

Table 1: Demographic and imaging summary statistics
Values are mean (SD) unless otherwise stated. WMH values are reported as geometric mean (SD). Symptomatic status as defined using global CDR: Presymptomatic = CDR score of 0 at both of their first two visits; Questionably symptomatic = CDR score of 0.5 at one or both of their first two visits (the other being 0 or 0.5); Symptomatic = CDR score of 1.0 or greater at one or both of their first two visits. Subgroups with an N<3 were excluded from the table for anonymity. [a] Adjusted for TIV

Methods - Image processing

❖ WMH were segmented using a semi-automated protocol (Fiford and Sudre et al., 2020)

❖ Brain atrophy rate was calculated using the boundary shift integral (BSI) (Leung, 2012)

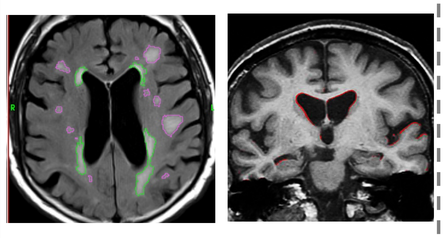


Figure 1: WMH segmentation and BSI examples
Examples of a) a semi-automated WMH segmentation and b) a BSI measurement

❖ Model 3: Mixed-effect linear regression: assessing the effect of estimated years to onset (EYO) on WMH accrual

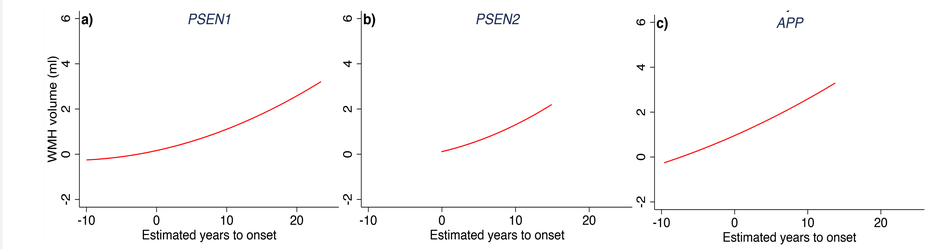
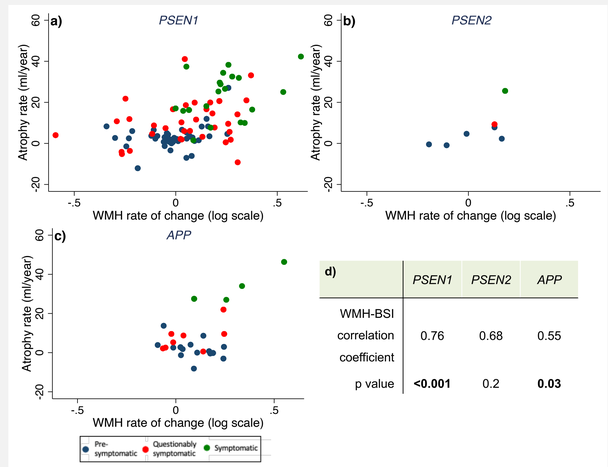


Figure 3: WMH accrual with estimated years to onset
Plots of WMH volume with expected years to onset in each mutation group. Fitted lines were calculated for each participant from a linear mixed-effects regression model with random slopes but fixed intercepts, and then averaged to give one fitted line per mutation group. Participants with an EYO less than -10 were excluded from these graphs.

- Preliminary findings from mixed-effects modelling suggest that there were linear increases in WMH volume with estimated years to onset in all three mutation groups (p<0.001, all tests).
- Preliminary findings from additional modelling including a quadratic term, suggest an acceleration of WMH accrual approaching and passing estimated onset of disease in the *PSEN1* and *PSEN2* groups (p=0.001, both tests)

❖ Model 4: Joint mixed-effect linear regression: estimating correlations between WMH change and brain atrophy rate



d)	*PSEN1*	*PSEN2*	*APP*
WMH-BSI correlation coefficient	0.76	0.68	0.55
p value	**<0.001**	0.2	**0.03**

Figure 4: Jointly-modelling WMH change with brain atrophy rate
Scatter plots a)-c) show the crude relationship between atrophy rate and WMH accrual rate for each mutation group, colour coded for symptom group. In d) a joint mixed model was used to estimate the correlation between atrophy rate and WMH change. Coefficients are estimates of the correlation between the residual rate of change in WMH and brain atrophy rate measured by BSI, after allowing mean rates of change in WMH and brain volume to depend on proximity to expected onset. Models were standardised to mean TIV. Note that the graphs in a)-c) are crude rates of change that are not produced from the model used for the correlations in table in d).

- WMH change is associated with progressive brain atrophy in the *PSEN1* and *APP* groups, allowing for the stage of disease.

Conclusions

1. Mutation type has an impact on WMH accrual, with *APP* mutation carriers in this cohort gaining more WMH over time.
2. WMH changes are an important biomarker in autosomal dominant familial AD with burden increasing with EYO.
3. WMH change and brain atrophy rate track together across the AD disease course.

❖Although WMH are common in normal ageing and are often attributed to pathologies such as cerebrovascular disease, this study in a young familial AD cohort demonstrates that WMH are a core feature of AD and could be an important biomarker of disease progression.

References:
Fiford and Sudre et al. 2020. Automated White Matter Hyperintensity Segmentation Using Bayesian Model Selection: Assessment and Correlations with Cognitive Change. *Neuroinformatics*.
Leung et al.. 2012. Consistent multi-time-point brain atrophy estimation from the boundary shift integral. *NeuroImage*

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