

# Characteristics of $\alpha$ -synuclein negative Parkinson's disease and dementia with Lewy bodies

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## Background

$\alpha$ -synuclein seeding amplification assays ( $\alpha$ -syn SAA) enable in vivo detection of Lewy body pathology.  $\alpha$ -syn SAA shows high diagnostic accuracy for Parkinson's disease (PD) and dementia with Lewy bodies (DLB) at neuropathology, with slightly lower performance in clinical cohorts.

**Objective:** Examine the characteristics of  $\alpha$ -syn SAA-negative participants with clinically suspected DLB and PD.

## Method

We included 403 participants from the BioFINDER cohorts, in whom PD or DLB had, at some point, been assessed as the most likely diagnosis; and in whom  $\alpha$ -syn SAA had been analysed in cerebrospinal fluid (CSF). The mean follow-up time was 3.96 years (SD 3.14; range 0–11.9 years), complemented by medical record review extending up to 17 years. Fifty-eight participants had whole-genome sequencing, including all NegPD. Longitudinal  $\alpha$ -syn SAA data were available for 17 of the negative participants

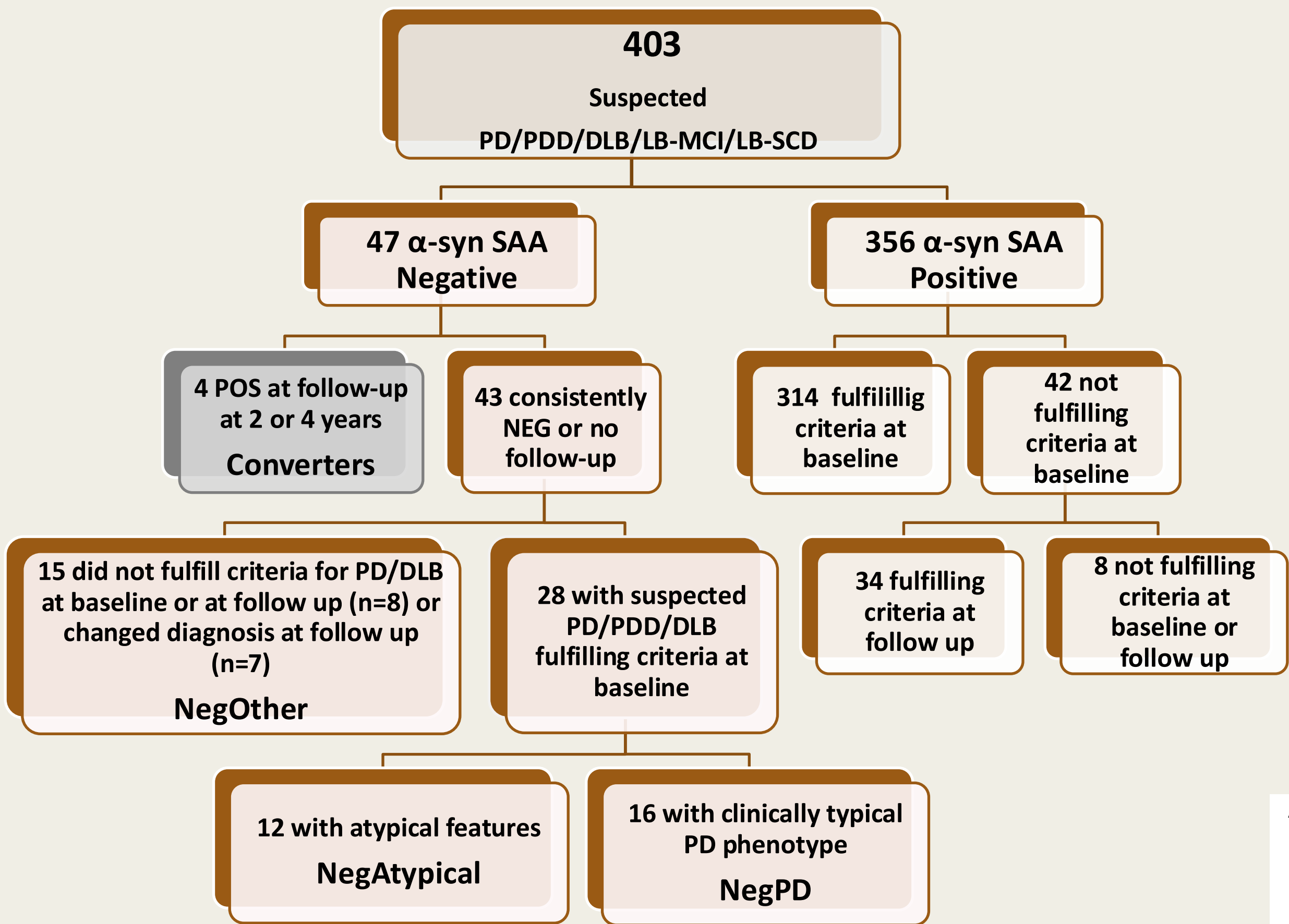


Figure 1) Flowchart of the 403 included participants.

## Results

Of the 403 participants, 47 were  $\alpha$ -syn SAA-neg. After review of available data; 4 groups of  $\alpha$ -syn SAA-neg were identified: i) participants not fulfilling formal diagnostic criteria or changed diagnosis “NegOther” (n=15); ii) fulfilled criteria at baseline but had atypical features “NegAtypical” (n=12); iii) participants fulfilling criteria for PD with typical PD phenotypes “NegPD” (n=16); participants converting from  $\alpha$ -syn SAA-negative to positive during follow-up “converters” (n=4) (Figure 1).

NegPD were younger, had less motor symptoms and lower CSF NFL. NegPD had better results on delayed 10-word recall but not on MMSE compared with Positive. NegPD and NegOther had significantly better olfactory function and less orthostatic hypotension. There were no differences in amyloid co-pathology (Figure 2). 5 of NegPD had at some point advanced neurosurgical treatment, compared with 25 Positive.

We did not identify any genetic variants associated with reduced or absent  $\alpha$ -syn SAA seeding activity in the NegPD or NegOther/NegAtypical groups (Table 1).

NegPD had slower cognitive decline on MMSE compared with Positive but  $\alpha$ -syn status did not significantly affect motor progression (Figure 3).

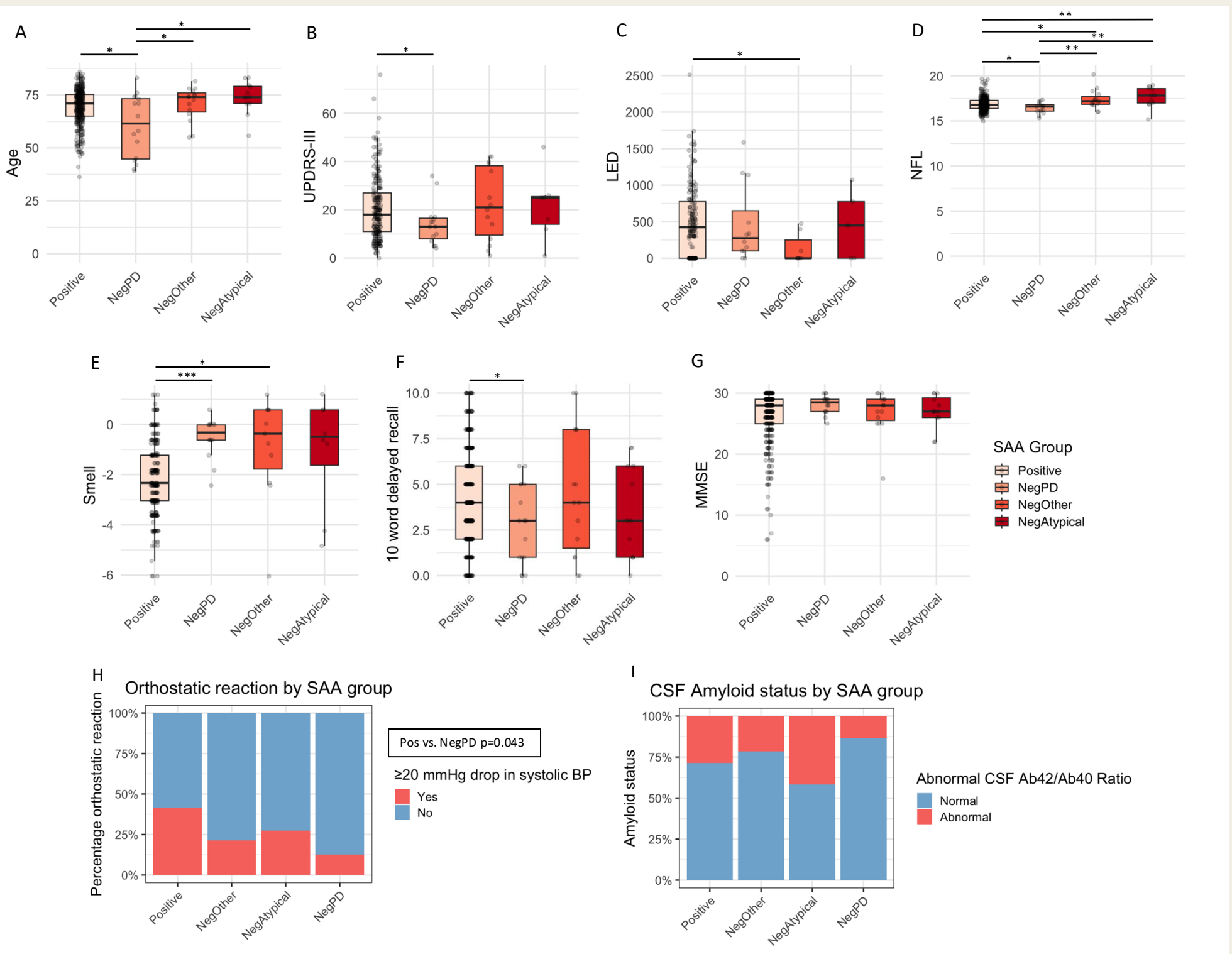


**Figure 2)** Boxplots depicting depicts mean and 95% confidence interval for A) Age, B) UPDRS-III motor score, C) Levodopa equivalent dose (LED), D) CSF-NFL normalized to Nulisa E) z-score of olfactory function, F) 10 word delayed recall, G) MMSE; Bar charts of percentages with H) Amyloid beta positivity measured by Ab42/40 ratio, I) Orthostatic hypotension defined as  $\geq 20$  mmHg drop in systolic blood pressure according to  $\alpha$ -syn SAA group. Significance levels: \*  $<0.05$ , \*\*  $<0.01$ , \*\*\*  $<0.001$ .

## Conclusion

We identify a group of  $\alpha$ -syn SAA-negative PD patients with a clinically typical phenotype, but with better olfactory function, slightly milder symptoms and better cognitive longitudinal outcome.

A negative  $\alpha$ -syn SAA result does thus not exclude a clinical diagnosis of PD, nor does it imply a lack of benefit from symptomatic treatments, including advanced therapies, but it warrants a careful clinical evaluation.

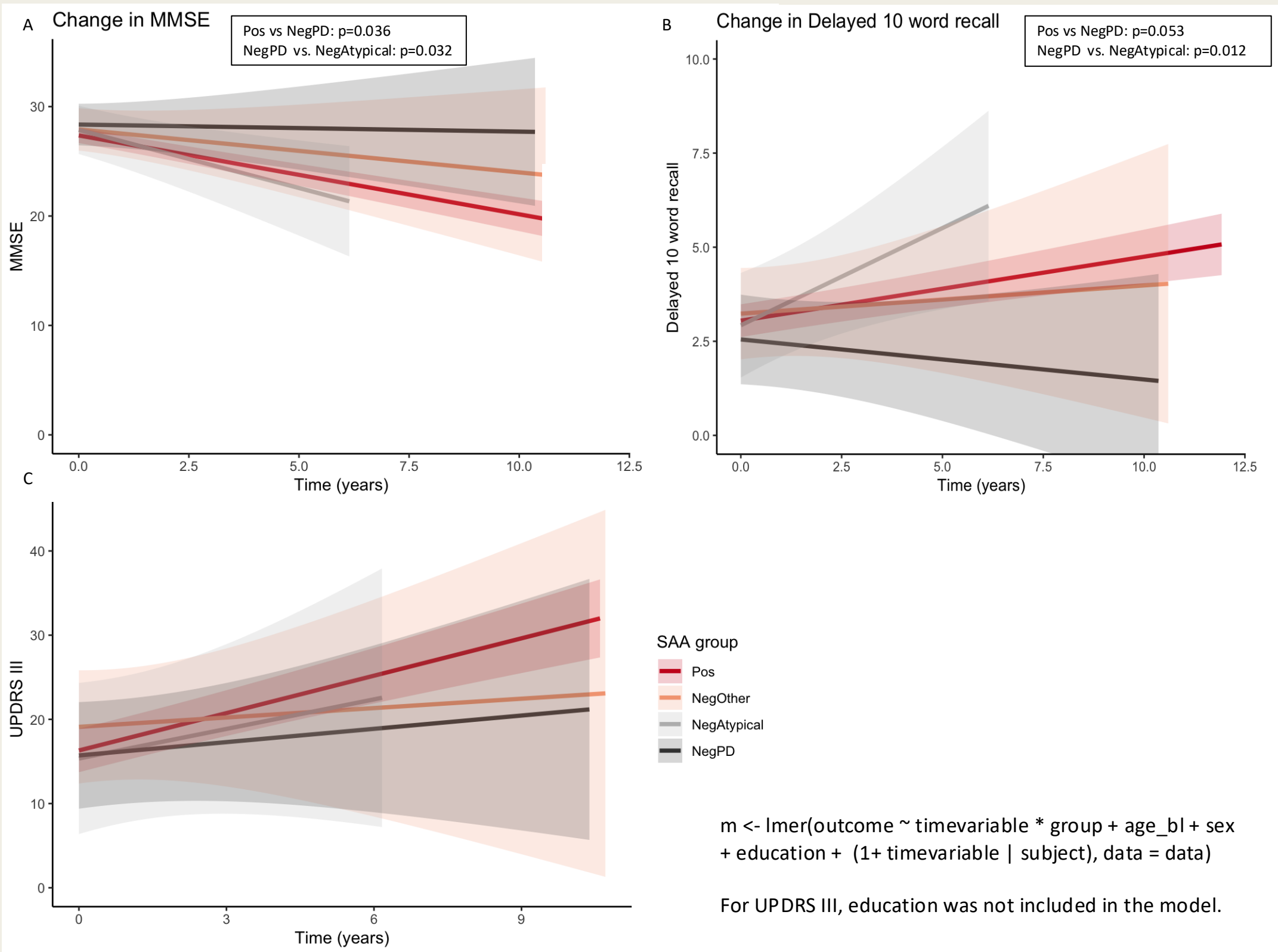


**Figure 3)** Longitudinal changes in A) MMSE, B) 10-word delayed recall and C) UPDRS-III motor score by  $\alpha$ -syn SAA group

**Table 1) Genetic analysis**

| $\alpha$ -syn SAA group | High-impact variants (ACMG-classification as “Pathogenic” or “Likely pathogenic”) | Low-to-medium impact variants (GBA1 variants) PD-related impact grade according to Parlar et al Mov Disord 2023 |
|-------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| Positive (n=26)         | LRRK2 p.(Gly2019Ser) in 1 individual<br>SNCA duplication in 1 individual          | GBA1 p.(Leu483Pro) [Severe] in 1 individual<br>GBA1 p.(Glu365Lys) [Risk variant] in 3 individuals               |
| Converter (n=3)         | LRRK2 p.(Arg1441Cys)* in 1 individual                                             | GBA1 p.(Glu365Lys) [Risk variant]* in 2 individuals                                                             |
| NegPD (n=16)            | ND                                                                                | GBA1 exon 5 deletion [Severe] in 1 individual<br>GBA1 p.(Glu365Lys) [Risk variant] in 2 individuals             |
| NegAtypical (n=6)       | ND                                                                                | GBA1 p.(Glu365Lys) [Risk variant] in 1 individual                                                               |
| NegOther (n=7)          | ND                                                                                | ND                                                                                                              |

\*One individual carried both LRRK2 p.(Arg1441Cys) and GBA1 p.(Glu365Lys).