Relationship between leisure activities and clinical severity in familial FTD

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Background

Lifestyle activities such as physical and cognitive activity have been shown to influence cognitive decline trajectories and mitigate disease progression in various forms of neurodegeneration. This has led to suggestions that such lifestyle factors may contribute to **cognitive reserve**, with increased reserve conferring a protective influence[1].

Prior work found that in **genetic frontotemporal dementia (FTD)**, participants with more active lifestyles showed less functional decline over time[2]. However, they had a limited follow-up sample size and did not compare activity between genetic groups.

This study aimed to examine whether lower levels of physical and/or cognitive activity were associated with **greater clinical impairment** in presymptomatic familial FTD, and to characterise longitudinal relationships between **activity and clinical progression** to assess potential cognitive reserve in familial FTD.

Methods

- 285 presymptomatic C9orf72, GRN, or MAPT mutation carriers + 193 non-carrier family relatives from the GENFI cohort completed the Physical Activity Scale for the Elderly (PASE) and Cognitive Activity Scale (CAS).
- The CDR+NACC FTLD-NM was used as a marker of clinical progression.

Table 1. Demographic data grouped by carrier status

Parameter	Non-carrier	Mutation carrier	
		Presymptomatic	Symptomatic
Age, years			
Mean±SD	49.2±13.8	45.7±12.6	62.3±7.2
Sex			
Female	104 (54%)	172 (60%)	21 (36%)
Male	89 (46%)	113 (40%)	38 (64%)
Genetic group, *n*			
C9orf72	73	151	38
GRN	87	96	7
MAPT	33	38	14
Education, years			
Mean±SD	15.7±3.1	15.3±3	13.2±3.5
CDR+NACC FTLD-NM SOB			
Mean±SD	0.2±0.6	0.5±1.2	10.2±5.6

Analyses performed

1) **Baseline presymptomatic comparisons** – Pearson's correlation and multiple linear regression (adjusted for age, sex, site, education covariates) were used to assess associations between activity levels and CDR score at baseline.

2) **Baseline presymptomatic high vs low activity groups** – participants were divided according to high and low activity levels and Wilcoxon rank-sum tests were used to compare the groups' CDR scores.

3) **Longitudinal CDR trajectories in all mutation carriers** – CDR change over time was examined using linear mixed effects models, adjusting for covariates.

Table 2. Participants with longitudinal data

	Baseline	Visit 2	Visit 3
Non-carrier	51	51	7
Presymptomatic	86	86	15
Symptomatic	14	14	4

Conclusions

- No differences in activity levels were observed between non-carriers and presymptomatic participants or C9orf72, MAPT, and GRN carriers.
- Lower levels of physical and cognitive activity were associated with greater clinical impairment in presymptomatic familial FTD.
- Physical activity was associated with slower clinical progression in carriers but did not modify trajectory in presymptomatic carriers alone.
- Cognitive activity was associated with significantly slower clinical decline in presymptomatic carriers alone.

References

1. Premi et al. (2017) Cognitive reserve and TMEM106B genotype modulate brain damage in presymptomatic frontotemporal dementia: a GENFI study. *Brain*. 140(6):1784-1791
2. Casaletto et al. (2020) Active lifestyles moderate clinical outcomes in autosomal dominant frontotemporal degeneration. *Alzheimers Dement*. 16(1):91-105

Results

There were significant differences between symptomatic participants and controls in both physical and cognitive activity levels ($p < .05$), but not between presymptomatic participants and controls. There were no significant differences in activity levels between non-carriers and genetic groups (MAPT, C9orf72, GRN).

1) Baseline presymptomatic comparisons

- Greater PASE scores were significantly related to lower CDR scores ($p < .001$)
- Greater CAS scores were significantly related to lower CDR scores ($p < .05$)

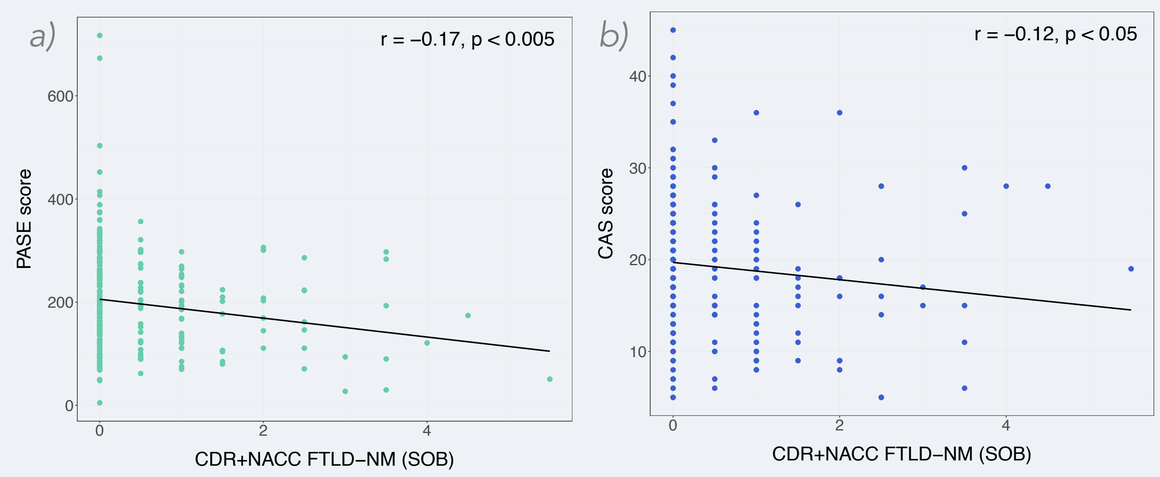

Figure 1. Higher a) physical and b) cognitive activity levels were significantly correlated with lower CDR scores

2) Baseline presymptomatic high vs low activity groups

- The low PASE group had significantly higher CDR +NACC FTLD-NM scores (mean±SD: 0.59±1.04) compared to the high group (0.29±0.67; $p = .005$).
- The low CAS group had significantly higher CDR +NACC FTLD-NM scores (mean ± SD: 0.60 ± 0.88) than the high group (0.38 ± 0.90; $p < .05$).

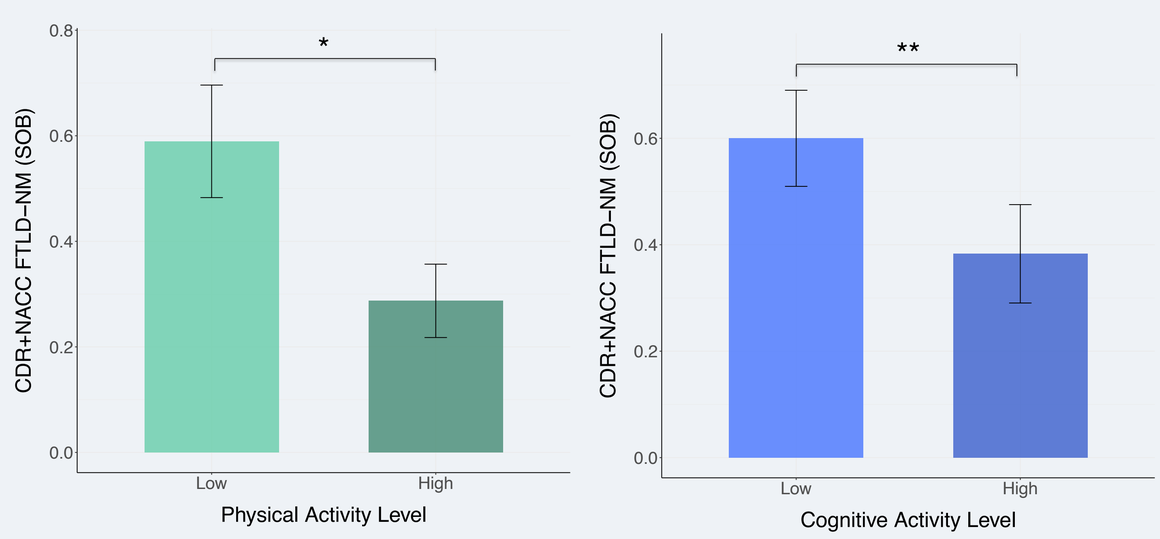

*Figure 2. CDR scores were significantly different between low vs high physical and cognitive activity groups * p < 0.05, ** p < 0.01, *** p < 0.001*

3) Longitudinal CDR trajectories in all mutation carriers

- Higher PASE score was associated with slower clinical decline ($p < .05$), and with lower baseline CDR severity ($p < .05$).
- PASE did not significantly modify slope in presymptomatic carriers alone.
- Higher CAS score was associated with lower baseline clinical severity ($p < .05$) and with significantly slower clinical decline in presymptomatic carriers alone ($p = .005$).
- The global Time × CAS interaction was not significant in carriers.

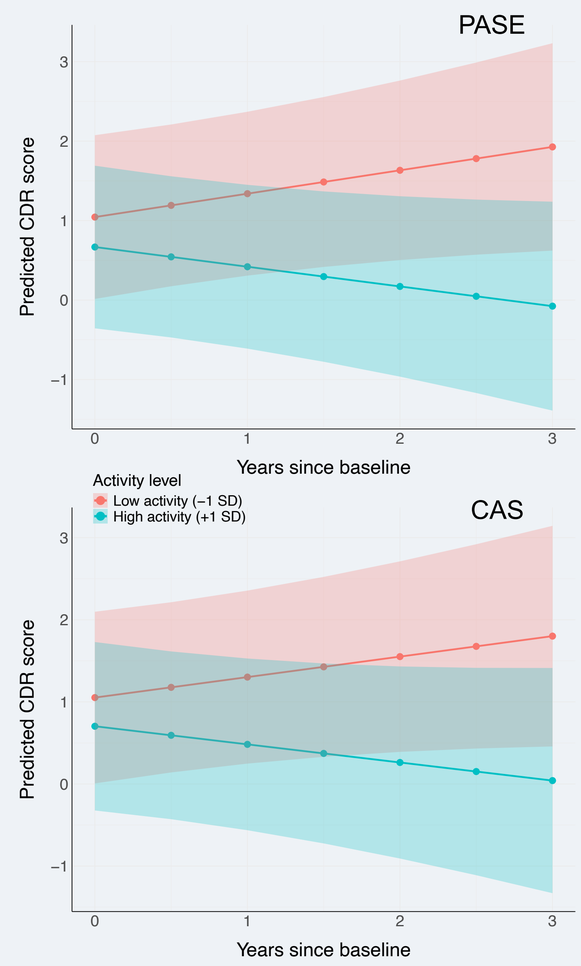

Figure 3. Model-based predicted CDR trajectory by activity level

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