# Can Non-pharmacological Interventions Change Levels Of Neurofilament Light And Phosphorylated-tau In Older Adults At Risk Of Dementia?

## Updated biomarker analyses from the SCD-Well randomized clinical trial

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## Background

- Older adults with subjective cognitive decline (SCD) are at increased risk of dementia.
- Blood biomarkers can help monitor neurobiological change in dementia-prevention trials.
- Neurofilament light (NfL) reflects neuroaxonal injury and downstream neurodegeneration; p-tau181 reflects AD-related tau biology.
- Non-pharmacological interventions may reduce dementia risk, but NfL and p-tau181 are rarely used as surrogate outcomes in prevention trials.

**First trial to use NfL as a surrogate endpoint in individuals with SCD**

## Aim

**To examine whether an 8-week mindfulness-based intervention or a health self-management intervention alter plasma NfL and p-tau181 in adults with increased dementia risk.**

## Study characteristics

| Baseline characteristic | HSMP (n=67) | CMBAS (n=70) |
|---|---|---|
| Age, years | 73.3 (5.9) | 72.1 (7.6) |
| Female sex | 41 (61%) | 44 (63%) |
| Education, years | 13.3 (3.5) | 13.9 (3.8) |
| NfL, pg/ml | 26.7 (15.3) | 24.1 (12.7) |
| p-tau181, pg/ml | 1.8 (1.1) | 1.7 (0.9) |
| Physical activity, PASE | 117.5 (65.2) | 132.0 (75.5) |
| Sites | UK/DE/ES/FR | UK/DE/ES/FR |

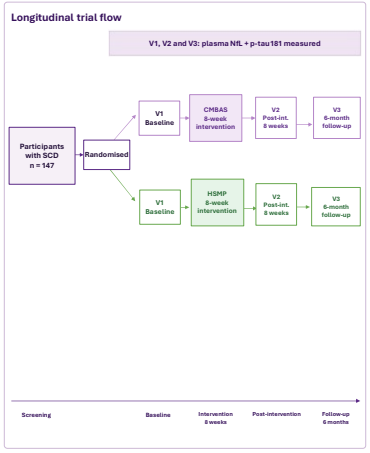
*Data are n (%) or mean (SD). Participants shown are those with ≥1 NfL value available.*

**147 older adults with SCD randomized across four European memory-clinic sites.**

## Methods

### Design and sample

- SCD-Well was an 8-week randomised controlled trial comparing a mindfulness-based intervention with a health self-management/education programme in older adults with SCD [Marchant et al., 2018].
- 147 randomized; 140 included in biomarker analyses; 7 did not consent to venepuncture.




*140 included in biomarker analyses*

### Interventions

**CMBAS** — Body scan, mindful movement, sitting meditation, and psychoeducation to manage cognitive concerns and worry.

**HSMP** — Based on previously published manual adapted and validated for SCD (Marchant et al., 2018). Structurally matched programme designed to promote health self-efficacy through sleep, stress, exercise, diet and future planning



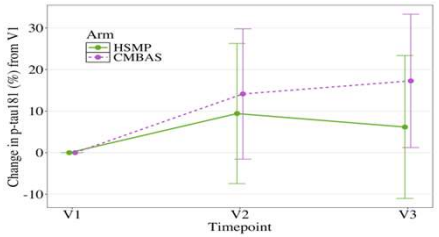

### Biomarkers and Statistical analysis

- Plasma NfL and p-tau181 measured at V1, V2 and V3 using SIMOA on a Quanterix HD-X analyser.
- Biomarkers were log-transformed for analysis.
- Linear mixed models tested visit-by-arm interaction and within-arm change. Both outcome models included the following covariates: age, sex, education, study site, APOE genotype, and baseline plasma Aβ42/40 ratio. The NfL model also adjusted for physical activity, BMI, and p-tau181 (all baseline) as well as history of kidney disease.
- The models reported here used observed data only. In sensitivity analyses, models were restricted to participants who attended a minimum of 4 sessions. In addition, modified intention-to-treat (mITT) analyses included all randomised participants who consented to blood sampling; missing biomarker data were imputed. Sensitivity and mITT results were consistent with observed data analyses.

## Results

### No significant visit-by-arm interaction for p-tau181

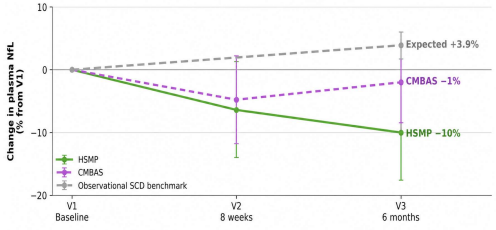
**Phosphorylated tau 181 (p-tau181): change from baseline over time**




CMBAS showed **a significant V1→V3 increase** (+0.17 log units; 95% CI +0.01 to +0.33), equivalent to 17% increase. CMBAS showed a somewhat smaller non-significant increase (6%).

### No significant visit-by-arm interaction for NfL; Significant HSMP V1→V3 reduction.

**Neurofilament light (NfL): change from baseline over time**




*Contextual benchmark only: observational data are not a randomized passive comparator.*

HSMP showed **a significant V1→V3 reduction** (−0.10 log units; 95% CI −0.20 to −0.00), equivalent to 10% reduction. CMBAS showed a smaller non-significant reduction (1%)

Observational benchmark: Observational studies of longitudinal plasma NfL levels in older adults without objective cognitive impairment suggests plasma NfL would be expected to rise over approximately 6 months, providing context for the reductions observed in SCD-Well.

Five studies (Baldacci et al., 2020; Chatterjee et al., 2022; Hu et al.,2019; Khalil et al., 2020; Verberk et al.,2021) included a total of 629 participants with a mixture of controls and people with SCD (See Appendix of OG paper for details).

NfL reductions are biologically interesting because observational cohorts suggests NfL would typically rise over similar follow-up.

Without neither a passive comparator nor significant visit-by-arm interaction, NfL reduction should be interpreted as possible attenuation of expected NfL increase rather than proof of intervention causality.

p-tau181 should be interpreted cautiously because short-term uncertainty/variability appears wider than for NfL (Brum et al., 2023)

## Interpretation

**Significant reduction in NfL at follow up; NfL and p-tau181 patterns indicate different pathways**

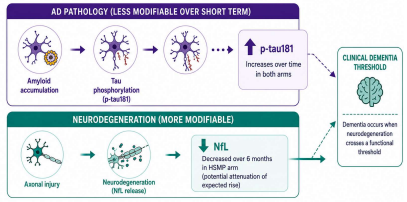
**NfL** — Broader neuronal injury, neuroaxonal damage and downstream neurodegeneration.

**p-tau181** — AD-related tau biology; may not mirror short-term changes in general neurodegeneration.

**Attenuating NfL-related neurodegeneration may help delay progression towards the clinical dementia threshold, even if underlying AD pathology continues to accumulate.**

### CONCEPTUAL FRAMEWORK: DIVERGENT BIOMARKER TRAJECTORIES

*A model for interpreting SCD-Well findings*




### Why might HSMP influence NfL?

The HSMP-related reduction in NfL may reflect lifestyle-related pathways.

In a previous SCD-Well secondary analysis, HSMP participants showed increased self-reported physical activity at follow-up compared with CMBAS participants (D'Elia et al., 2024).

This is relevant because modifiable lifestyle factors e.g. physical activity can influence innate immune responses and microglia-driven inflammation in ageing brains (Duggan & Parikh, 2021). However, this interpretation remains exploratory and further research is required to evaluate this.

## Limitations

- No passive comparator.
- Short follow-up.
- Study designed for primary outcome: anxiety

## Conclusions

- We observed a reduction in NfL over 6 months in individuals who had participated in an 8-week HSMP programme.
- p-tau181 increased over time in both arms and did not mirror NfL change.
- Findings suggest non-pharmacological interventions may have measurable biological effects!
- Longer trials with passive comparators, extended follow-up and clinical endpoints are needed to clarify this.

**Scan for the accompanying paper (NfL data only)**

**References**

Marchant et al. (2018). DOI:10.1016/j.trci.2018.10.010.
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