Neuropsychiatric burden is related to increased amyloid and tau deposition in late middle-aged cognitively normal individuals with a family history of Alzheimer’s disease

**BACKGROUND AND OBJECTIVES**
Cognitive lifestyle factors (e.g., education, cognitive activity) and neuropsychiatric factors (NPF) (e.g., anxiety, depression) are associated with an increased risk of Alzheimer’s disease (AD) (Livinston et al., 2017). Recent evidence has also linked personality traits with progression to AD dementia (Terracciano et al., 2017). The relationships between those factors and AD pathologies along with other brain correlates still remain to be understood better in the preclinical phase of the disease. We investigated whether combinations of cognitive lifestyle factors (e.g., education, cognitive activity) and NPF & personality traits are related to AD pathology (amyloid [Aβ] and tau deposition) and brain function in cognitively normal older adults at risk of AD.

**PARTICIPANTS**
Cognitively normal older adults with a family history of AD (PREVENT-AD study)

<table>
<thead>
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<th>Mean ± sd (range)</th>
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<td>Age at PET</td>
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<tr>
<td>Gender F:M (%)</td>
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<td>APOE4 carriers (%)</td>
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<td>Global Aβ SUVR</td>
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<td>Entorhinal tau SUVR</td>
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**BEHAVIORAL FACTORS**
- Years of education
- Mean lifetime cognitive activity (Wilson et al., 2003)
- Social isolation (Donat & Ware, 1984)
- Geriatric Depression Scale (Yesavage et al., 1983)
- Geriatric Anxiety Inventory (Pachana et al., 2007)
- Stress Subscale (Lovibond and Lovibond, 1995)
- Apathy Evaluation Scale (Martin and Bodzryczky, 1991)

**PERSONALITY TRAITS**
- Big Five Inventory (John, Donahue and Kentle, 1991)

**NEUROIMAGING**
PET images were normalized by the cerebellum gray matter for Aβ and interior cerebellum gray matter for tau

**ANALYTICAL METHODS**
1. Partial least squares (PLS) analyses were used to evaluate the relationship between cognitive lifestyle, NPF & personality traits (behavioral factors) and AD pathology (Aβ and tau, separately). The partial least squares were assessed with a p-value determined by permutation tests.
2. To try to identify potential brain correlates associated with behavioral factors and AD pathology, we assessed the relationships between behavioral factors composite scores derived from the PLS and within-network functional connectivity, and how AD pathology might moderate these relationships.

**CONCLUSIONS**
Our multivariate approach revealed that different combinations of behavioral factors are related to Aβ and tau burden in cognitively normal older adults at risk of AD.

The relationships between those combinations of behavioral factors and functional connectivity were differently affected by Aβ and tau. Those results are in line with accumulating evidence of Aβ being related to hyperconnectivity and tau to local hypoconnectivity (Sepulcre et al., 2017; Schultz et al., 2017). Overall, our results suggest the importance of combining factors to identify relationships with early AD-related pathology and highlight the relevance of incorporating broader factors in preventive strategies.