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## TITLE PAGE

### **Subtle postoperative cognitive disorder in preclinical Alzheimer's disease**

Running title: Subtle POCD in preclinical AD

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## AUTHOR CONTRIBUTION

P. Glasman participated in study concept & design, data acquisition, analysis & interpretation

M. Houot conducted the statistical analysis & interpretation

G. Gagliardi participated in data acquisition and analysis (cognitive data)

MO Habert participated in data acquisition and analysis and critical revision of the manuscript for important intellectual content

R. Migliaccio and S. Bombois participated in critical revision of the manuscript for important intellectual content

F Cacciamani participated in critical revision of the manuscript for important intellectual content

B Dubois participated in critical revision of the manuscript for important intellectual content and study supervision

S Epelbaum participated in study concept & design, interpretation of analysed data and study supervision

## ABSTRACT

**Background:** We examined the association between preclinical Alzheimer's disease (AD) and undergoing anaesthesia and surgery ("surgery" henceforth) in a cohort of elderly individuals with a subjective cognitive decline (SCD).

**Methods:** Individuals with SCD (N=268) were enrolled in a longitudinal follow-up study. Participants underwent comprehensive yearly cognitive evaluation for a period of 4 years. Brain amyloid load and glucose metabolism were studied by 18F-Florbetapir and Fluorodeoxyglucose positron emission tomography (PET) at baseline and after two years of follow-up. Exposure to surgery was systematically assessed during the first two years of follow-up. The association between surgery, cognition and AD markers was evaluated using generalized linear mixed models for cognition and linear models for neuroimaging markers.

**Results:** Sixty-five participants (24.25%) underwent surgery during the first year of follow-up, and 43 (16.04%) during the second year. Undergoing surgery had no overall impact on cognition over 4 years of follow-up nor on amyloid load and brain metabolism at two years of follow-up. However, a second step analysis revealed a small but significant association between undergoing surgery and a subtle decline in executive functions such as mental flexibility and divided attention (TMT B-A), in participants with greater amyloid load at baseline (Cohen's  $f^2=0.01$ , multiple comparison corrected  $p<0.001$ ). Highly educated participants with surgery had significantly decreased metabolism over two years, when compared to low educated participants (Cohen's  $f^2=0.04$ ,  $p=0.031$ ).

**Conclusions:** Our results suggest that surgery is associated with an increased risk of subtle cognitive decline after surgery, in the cognitively healthy elderly at risk for AD.

Keywords: post-operative cognitive disorder, preclinical Alzheimer disease, Longitudinal cohort study, Amyloid imaging, generalized linear mixed models, linear models.

## INTRODUCTION

Postoperative cognitive disorder (POCD) is a common post-surgical neurological condition affecting mortality, autonomy, and quality of life <sup>1, 2</sup>, with an incidence between 15% and 40% <sup>3-5</sup>.

Due to improvements in the management of surgery and anaesthetics, and the aging of the population of high- income countries, almost half of the surgical patients in these countries are now older than 65 years <sup>6</sup>. The prevalence of patients with preoperative Alzheimer's disease (AD), the most frequent neurodegenerative disease in elderly population, is increasing. Preoperative AD dementia has been shown to be associated with POCD <sup>7, 8</sup> but this association remains to be discovered in preclinical AD. To this day, the most definitive study of POCD showed a "small additional cognitive decline, equivalent on average to less than five months of aging" in a longitudinal study spanning 19 years, though AD biomarkers were not used <sup>9</sup>. However, another study reported an association between cerebrospinal fluid (CSF) beta-amyloid (A $\beta$ ) and POCD. <sup>10</sup>

Recent consensual definitions of preclinical AD state that this stage of the disease can be considered in cognitively healthy individuals as the presence of positive biomarkers of Alzheimer pathology <sup>11, 12</sup>, including CSF A $\beta$ , tau and phosphorylated tau analyses, and positron emission tomography (PET) imaging of amyloid plaques and tau pathology.

Our aim was to disentangle the association between preclinical AD and POCD, in a large cohort of elderly individuals, cognitively normal at baseline, who underwent a neuropsychological evaluation, and cerebral amyloid and metabolic PET scans. Specifically, we surmised that the previously described link between preclinical AD and POCD was biased, since individuals with positive AD biomarkers are more prone to display cognitive impairment which was not always accounted for before the surgery.

## MATERIALS AND METHODS

INSIGHT-PreAD study is a mono-centric study aimed at determining the factors that increase the risk of progression of cognitively normal elderly individuals with a known amyloid status to clinical AD. INSIGHT-PreAD enrolled 318 participants between 70 to 85 years of age, with a subjective cognitive decline (SCD) and no objective cognitive disorders (mini-mental state examination score MMSE  $\geq 27$  and total recall score in the free and cued selective reminding test FCSRT  $\geq 41$ ). Exclusion criteria included clinical dementia rating scale (CDR)  $> 0$ , visual and auditory functions inadequate for neuropsychological testing, and the existence of a known neurological disease, recent stroke and illiteracy. Participants have a 5-year longitudinal follow-up, with annual comprehensive neuropsychological evaluation, and MRI and amyloid PET imaging every 2 years. The study was approved by the local ethical committee (ANSM 130134B-31) and all participants signed a written informed consent. By October 2019, all participants had completed the fourth year of follow-up.

### Collection of surgical data

All surgical procedures occurring during the follow-up were systematically recorded as adverse events. In addition, to maximize data collection and homogeneity, all participants were contacted by phone to recover information about any anaesthesia/surgery that occurred through a standardized questionnaire by an anaesthesiologist (PG). For those who were exposed to surgery, we collected data about the type of anaesthesia, type of surgery, medical indication for surgery, hospital stay length, and postoperative complications. We considered cardiac, thoracic, vascular, laparotomy, major fracture surgeries and knee and hip replacement as major surgery. Minor surgeries included outpatient surgery, surgery followed by less than 2 days of hospitalization, eye, skin, or endoscopic procedures. No participant underwent brain surgery nor cerebrovascular surgery. Only one participant had surgery both between M0 and M12 and between M12 and M24. As the groups are mutually exclusive, he was included in the M0M12 group. Since it concerns only one participant, we do not consider this fact to have an impact on our general findings.

### Neuropsychological testing

A comprehensive neuropsychological examination was performed every year in the Insight Pre-AD cohort. In the present study, we focused on a subset of these scores, namely on the mini mental state examination (MMSE) as a measure of global cognitive functioning; the free and cued selective reminding test (FCRST) assessing episodic memory; the Frontal assessment battery (FAB) assessing executive functions; the Trail making test B-A (TMT B-



A) assessing mental flexibility and divided attention; and verbal fluency tasks assessing lexical access abilities.

### Biomarkers of AD

All individuals from the INSIGHT-PreAD cohort underwent <sup>18</sup>F-AV-45 (Florbetapir) PET scan at baseline (M0) and M24, with high affinity for A $\beta$  plaques.

All Florbetapir-PET scans were acquired in a single session on a Philips Gemini GXL scanner at 50 ( $\pm$  5) minutes after injection of approximately 370 MBq (10 mCi) Florbetapir. Florbetapir-PET acquisition consisted of 3 x 5 minutes' frames, a 128 x 128 acquisition matrix and a voxel size of 2 x 2 x 2 mm<sup>3</sup>. Images were then reconstructed using iterative LOR-RAMLA algorithm. Lastly, frames were realigned, averaged and quality-checked by the CATI team (<http://cati-neuroimaging.com>). Structural MRI scans were segmented and spatially normalized in the MNI space using the VBM8 package (<http://dbm.neuro.uni-jena.de/vbm/>) implemented in SPM8 (Institute of Neurology, London, UK; <http://www.fil.ion.ucl.ac.uk/spm/>). Deformation fields, grey and white matter masks were generated and further used to define regions of interest (ROI). Florbetapir-PET images were coregistered to structural MRI images using SPM8 with visual inspection to detect any coregistration errors. Using inverse deformation fields and matrix transformation, a composite cortical ROI, including both left and right precuneus, posterior cingulum, anterior cingulum, parietal, temporal and orbitofrontal cortices, were placed in the individual native PET space. The same step was done with a reference region (RR), composed of pons and whole cerebellum. After correcting for partial volume effect with the RBV-sGTM method <sup>19</sup>, parametric PET images were created for each individual, by dividing each voxel by the mean activity extracted from the RR. Finally, standard uptake value ratios (SUV<sub>r</sub>) were calculated by averaging the mean activity of all ROIs in the individual PET native space. All these steps were done with an automated pipeline developed by the CATI engineers and were quality-checked by the CATI team. The SUV<sub>r</sub> threshold to determine abnormality uptake was extracted performing linear correlation between our developed method and the method used by Besson et al. <sup>13</sup>, using PET images from the IMAP cohort.

The same image-assessment pipeline was applied at M0 and M24 to measure brain glucose metabolism on <sup>18</sup>F-FDG PET scans. Cortical metabolic indices were calculated in four bilateral regions of interest that are specifically affected by AD <sup>14</sup>: posterior cingulate cortex, inferior parietal lobule, precuneus, and inferior temporal gyrus, and the pons was used as the reference region

## Statistical analysis

We used 3 different statistical approaches.

Firstly, we used  $\chi^2$  test for categorical variables and Kruskal-Wallis test for numerical variables, in order to compare demographic (gender, age, education, ApoE genotype) and clinical characteristics (surgery characteristics, AD biomarkers, cognitive scores) between three groups of subjects: (i) No surgery; (ii) Operated during the first year of follow-up; (iii) Operated during the second year. When the global test was significant, pairwise Wilcoxon-Mann-Whitney test was performed for numerical variables and pairwise  $\chi^2$  test for categorical variables, both with Benjamini-Hochberg correction, to investigate which group(s) differed from the other(s).

Secondly, we performed generalized linear mixed models (GLMMs) to compare the longitudinal changes of cognitive scores over the 4 years of study between the three groups: (i) No surgery; (ii) Operated during the first year; (iii) Operated during the second year. The fixed effects were: group; mean amyloid load; mean brain metabolism; visit; gender; age at baseline; education level (defined as high if the participant had at least his/her high school diploma, and low if not). A random intercept was included for the subjects. We also investigated several interactions: (i) Visit X Group, to study if cognitive changes were different between groups; (ii) Visit X Amyloid and Visit X Metabolism, to study if variations on biomarker at baseline can impact cognitive changes; (iii) Group X Amyloid and Group X Metabolism, to study if the biomarkers at baseline had a different effect on cognitive performance between groups; (iv) Visit X Group X Amyloid and Visit X Group X Metabolism, to study if the biomarkers at baseline had a different effect on cognitive trajectories between groups. We considered three different amyloid values: the cut off score used to determine “amyloid positivity”<sup>19</sup> and two extreme values (the 5th and 95th percentiles respectively) to analyse low and high amyloid profiles.

In these analyses, cognitive functioning was measured using lexical and semantic fluencies (with Poisson family and logarithmic link in the GLMMs), the TMT B–A (with Normal family and identity link), and the MMSE and FCSRT total recall score with (Binomial family and logit link for both).

Main effects and interaction were tested using type II likelihood ratio tests. Cohen's  $f^2$  were calculated to estimate effect size. P-values were corrected for multiple testing using Benjamini-Hochberg procedure, as we assessed cognitive decline using 5 scores.

We additionally performed an analysis taking into account perioperative variables such as “major surgery yes/no”, “hospitalization duration” and “time since surgery”. Finally, we analyzed the impact of co-morbidities (namely hypertension, diabetes, hypercholesterolemia and smoking, as already assessed in the Insight PreAD cohort. See Mendes et al <sup>15</sup>) by computing a model including these co-morbidities as variables. Only the postsurgical time points were considered in the analyses.

Thirdly and finally, we performed two linear models (LMs) to evaluate the impact of surgery on the longitudinal changes of amyloid load and brain metabolism. The dependent variable was the percentage of change of the biomarker between baseline and after two years. The independent variables were group (“operated” or “not operated”); biomarker value at baseline; gender; age at baseline; and education level. All second order interactions were tested independently and added in the final model if significant. The interaction between biomarker value at baseline and group was forced in the final model. Type II F-tests were used to test main effects and interactions. Cohen's  $f^2$  were calculated to assess effect sizes. Normality of residuals and heteroskedasticity were checked visually. Cook's distances were computed to investigate potential influencers and outliers. Analyses were performed by removing the subjects with Cook's distances greater than 1.

Statistical analyses were performed using R 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>). Packages lme4 version 1.1-17 and emmeans version 1.2 were used respectively to compute GLMMs and to plot the estimated marginal means.

## RESULTS

### Demographical characteristics of the cohort

Between May 2013 and January 2015, 318 community-based participants were enrolled in the INSIGHT-PreAD cohort. Among them, we collected surgical data for 268 participants (Supplementary Figure 1). The mean age ( $\pm$  standard deviation, SD) of our sample was 75.8 ( $\pm$  3.5) years, and 60.8% were women, with high educational attainment (70.5%). Among these participants, 65 (24.3%) underwent surgery at least once during the first year (only one subject with two surgeries) and 43 (16.0%) during the second year. we compared the participants included in this specific study and those who did not participate (50 vs 268). There were less women included (76% in the non-included vs 61% in the included group  $p = 0.041$ ) and also those who did not participate were older ( $77.1 \pm 3.4$  vs  $75.8 \pm 3.5$ ,  $p=0.01$ ) and were less educated (48% vs 29% of low educational level,  $p=0.01$ ).

### Comparison of demographic and clinical characteristics between groups

The characteristics of the three groups (i.e., No surgery; Operated during the first year; Operated during the second year) are detailed in Table 1. At baseline, participants operated upon during the first year were older than those with no surgery ( $76.8 \pm 3.7$  vs  $75.5 \pm 3.4$  respectively,  $p=0.028$ ), had better performances in FCSRT Free Recall (Operated during the first year:  $31.6 \pm 5.5$  vs No surgery:  $29.6 \pm 5.3$ ,  $p=0.041$ ) and and Fluencies in P (Operated during the first year:  $24.4 \pm 5.7$  vs No surgery:  $22.1 \pm 5.7$ ,  $p=0.018$ ; Operated during the first year:  $24.4 \pm 5.7$  vs Operated during the second year:  $21.4 \pm 6.5$ ,  $p=0.022$ ). Moreover, participants operated upon during the second year were more likely to have a lower education level than participants with no surgery (44.2% vs 24.4% respectively,  $p=0.049$ ).

Table 1: Study sample characteristics at baseline

	No Surgery (& N = 160 (59.7%)	M0M12 (# N = 65 (24.25%)	M12M24 (\$ N = 43 (16.04%)	p
Gender				0.237
- Male	69 (43.12%)	23 (35.38%)	13 (30.23%)	
- Female	91 (56.88%)	42 (64.62%)	30 (69.77%)	
age at baseline	75.00 [73.00, 78.00] <sup>#</sup>	77.00 [75.00, 79.00] <sup>&amp;</sup>	76.00 [74.00, 77.50]	0.024*
Educational level				0.035*
- High (>11 years)	121 (75.62%) <sup>§</sup>	44 (67.69%)	24 (55.81%) <sup>&amp;</sup>	

- Low (<12 years)	39 (24.38%)	21 (32.31%)	19 (44.19%)	
ApoE ε4				0.193
- absence	127 (79.38%)	57 (87.69%)	32 (74.42%)	
- presence	33 (20.62%)	8 (12.31%)	11 (25.58%)	
Follow-up duration after surgery (days)		198.00 [103.00, 272.00]	207.00 [91.50, 294.50]	0.526
Major surgery				0.741
- No		49 (80.33%)	34 (82.93%)	
- Yes		12 (19.67%)	7 (17.07%)	
Hospitalization duration (days)		1.00 [1.00, 3.00]	1.00 [1.00, 2.00]	0.952
Type of surgery				0.869
- Orthopedic		18 (27.69%)	14 (32.56%)	
- Coloscopy		15 (23.08%)	13 (30.23%)	
- Cataract		14 (21.54%)	5 (11.63%)	
- Digestive		5 (7.69%)	3 (6.98%)	
- Dermatologic		2 (3.08%)	2 (4.65%)	
- Urologic		4 (6.15%)	1 (2.33%)	
- ENT		2 (3.08%)	1 (2.33%)	
- Vascular		3 (4.62%)	1 (2.33%)	
- Gynecologic		1 (1.54%)	2 (4.65%)	
- Ophthalmologic		1 (1.54%)	1 (2.33%)	
Anesthesia				0.366
- General		42 (64.62%)	31 (72.09%)	
- Sedation		14 (21.54%)	5 (11.63%)	
- Loco-regional		9 (13.85%)	6 (13.95%)	
- Hypnosis		0 (0.00%)	1 (2.33%)	
At baseline				
Amyloid SUVR global	0.71 [0.67, 0.81]	0.73 [0.68, 0.80]	0.71 [0.67, 0.78]	0.371
Mean FDG	2.41 [2.28, 2.59]	2.43 [2.22, 2.56]	2.54 [2.30, 2.65]	0.235
MMSE	29.00 [28.00, 29.00]	29.00 [28.00, 29.00]	29.00 [28.00, 29.00]	0.715
FCSRT Free Recall	29.00 [26.00, 33.00]	32.00 [28.00, 35.00]	31.00 [27.00, 34.50]	0.050*
FAB	16.50 [15.00, 18.00]	17.00 [16.00, 18.00]	17.00 [16.00, 18.00]	0.289
TMTB-TMTA (time in seconds)	43.00 [25.00, 56.25]	35.00 [21.75, 54.25]	44.00 [28.75, 62.75]	0.267
Fluencies in P in 2 minutes	22.00 [18.00, 26.25] <sup>#</sup>	25.00 [20.50, 28.00] <sup>&amp;,\$</sup>	20.50 [17.25, 24.75] <sup>#</sup>	0.004*
Fluencies in animal names in 2 minutes	30.00 [26.00, 36.00]	32.00 [28.00, 37.50]	31.50 [26.25, 36.75]	0.566

M0M12: participants who underwent surgery in the first year of follow-up; M12M24: participants who underwent surgery in the second year of follow-up; ENT: ear nose and throat; SUVR: Standard uptake value ratio; MMSE: Mini mental state examination; FCSRT: Free and cued selective reminding test; FAB: Frontal assessment battery; TMT: trail making test. Median [quantile 25%, quantile 75%] or number (percentage) are

provided. To compare the three groups, we used  $\chi^2$  test for categorical variables and Kruskal-Wallis test for numerical variables. Post hoc tests were performed to compare each pairwise group :  $\chi^2$  test for categorical variables and Wilcoxon-Mann-Whitney test for numerical variables with Benjamini-Hochberg correction. Following signs indicate which groups significantly differ: & group differs from 'No Surgery'; # group differs from 'M0M12'; \$ group differs from 'M12M24'.

### **Effect of surgery on cognitive performance over the 4 years**

The cognitive performance of the three groups did not significantly change during the 4 years of study (Figure 1, Table S1). However, the evolution of the TMT B-A was significantly different between the three groups after taking into account the amyloid load at baseline (Cohen's  $f^2=0.01$ , multiple comparisons corrected  $p<0.006$ ). In particular, the impact of amyloid load on the longitudinal trajectory of TMT B-A score was different between the groups (Figure 2). Perioperative variables had no overall impact on these results (Table S2). Furthermore, adding comorbidities to the GLMMs did not change the significance of the results (Table S3).

Participants who did not undergo surgery had no change in any cognitive score over the 4 years, regardless of their amyloid load. The same applies to operated participants with a low amyloid load. However, as the amyloid load increased, the TMT score increased more over time after surgery. In summary, there was a synergistic effect of amyloid load and surgery on executive functions.

### **Effect of surgery on amyloid load and brain glucose metabolism**

Table 2 shows the effect of surgery on AD biomarkers after 2 years.

Surgery had no main effect on the percentage of change of amyloid load or brain metabolism during the 2 years of follow-up. On the contrary, the interaction between education and the surgery group had a significant effect on brain metabolism (Cohen's  $f^2=0.04$ ,  $p=0.003$ ). In particular, the brain metabolism of operated-upon subjects with high education significantly decreased over time (Supplementary Figure 2). Moreover, subjects with higher baseline metabolism also had higher rate of metabolism decrease.

Table 2: Results of linear models on the impact of surgery on Alzheimer's disease biomarkers evolution

	AV45 PET change (R2aj = 0.01)			FDG PET change (R2aj = 0.23)		
	coefficient ± se	Cohen's f <sup>2</sup>	pvalue	coefficient ± se	Cohen's f <sup>2</sup>	pvalue
Intercept	3.13 ± 2.41			29.05 ± 5.36		
Age	0.03 ± 0.10	<0.01	0.781 1	-1.98 ± 1.10	<0.01	0.4533
Gender (F)	-1.08 ± 0.72	0.01	0.136 6	-0.97 ± 0.77	0.01	0.2050
Education (high)	0.64 ± 0.79	<0.01	0.419 8	-1.08 ± 1.08	0.01	0.1654
BM at baseline	0.68 ± 3.53	0.01	0.178 7	-14.84 ± 2.48	0.24	<0.000 1*
Surgery group (No)	-5.47 ± 3.93	<0.01	0.975 9	-1.64 ± 7.75	<0.01	0.9172
BM at baseline * surgery group (No)	8.16 ± 5.74	0.01	0.156 7	-0.10 ± 3.63	<0.01	0.9775
Age * BM at baseline				0.83 ± 0.53	0.01	0.1154
Age * surgery group (No)				0.41 ± 0.22	0.02	0.0590
Education (high) * surgery group (No)				4.76 ± 1.59	0.04	0.0031 *

Coefficients and standard error (se) were extracted from complete LMs with all interactions. For categorical effects, the reference category is indicated in bracket. R2aj : adjusted coefficient of determination. F : Female, BM : biomarker (i.e. AV45 or FDG PET), No: Not operated

<sup>§</sup> For each main effect, the Cohen's f<sup>2</sup> was calculated without higher order interactions.

## DISCUSSION

This study of 268 cognitively-normal elderly people at-risk for AD, we found that having undergone a surgical operation was not associated with an overall cognitive decline over the 4 years of follow-up. However, in a secondary analysis we found an association between surgery and a subtle gradual impairment in executive functions such as mental flexibility and divided attention (TMT B-A) in participants with higher amyloid load at baseline.

To date, the association of preclinical AD with POCD remains debated. With the aging of the general surgical population, preclinical AD will concern more and more patients undergoing surgery<sup>16</sup>. In earlier studies<sup>10, 17</sup>, A $\beta$  biomarker sampling in the CSF yielded contradictory results concerning the link between amyloid status and POCD. This is probably explained by the absence of preoperative cognitive testing as a confounding factor, as in the Wisconsin Registry for Alzheimer's Prevention study<sup>18</sup>. As lower CSF A $\beta$  is associated with poorer cognitive functioning, in turn linked to POCD, the relationship between amyloid status and POCD in these previous studies is probably indirect and mediated by a preoperative cognitive impairment. In our study, controlling for a normal baseline (i.e. baseline cognitive assessment in individuals operated at the second year of study) allows us to advocate for a very subtle association between brain amyloid status and POCD in asymptomatic elderly individuals. In a large cohort of 8,503 twins, Dokkedal et al<sup>20</sup> have shown that there was no clinically significant association of major surgery and anaesthesia with POCD, suggesting that factors other than surgery and anaesthesia are more important for cognitive decline. Our results are partially in line with this study as the effect size of the executive function decline was small and evidenced only in the participants with high amyloid load. Two recently published studies from the Mayo Clinic Study of Aging described long-term cognitive trajectories in older adults that were similar to ours<sup>21, 22</sup>: in these two studies, the magnitude of the association of surgery with cognitive decline or cortical atrophy on MRI was also small, although it seemed to be higher compared to our findings. This may be due to the fact that operations in the 20 years prior to the neurological follow-up were considered, meaning that a very subtle effect in the few months following surgery like the one we found can become more important over time. Interestingly, a previous study by the same group found no association between surgery and long-term cognitive dysfunction<sup>23</sup>, due probably to the longer follow-up in the 2018 and 2019 articles which is necessary to demonstrate a subtle decline. Finally, the 19-year follow-up of Whitehall II cohort study showed a subtle cognitive decline, very much reminiscent of our findings<sup>9</sup>. What our study adds is the identification of a cognitive impairment that we associated with surgery within the same follow-up duration. Also, previous debate about the



existence of an association between surgery and cognitive decline/AD was probably due to the heterogeneity of the definition of POCD . Whereas acute postoperative delirium is well defined (by the DSM V ) and easily diagnosed (by the Confusion Assessment Method), this was not the case of late cognitive disorder. This prevented a general interpretation of research findings. A standardised definition for POCD has been recently proposed and is likely to promote reproducible research in the field <sup>24</sup>.

Interestingly, neither perioperative variables nor co-morbidities changed the aforementioned findings. Although this may be due to a lack of power, we may also surmise that the subtle effect that we showed is not entirely mediated by the co-morbidities leading to surgery, but genuinely by the anaesthesia and surgical procedure themselves.

A second important finding in our study is the absence of a statistically significant association between surgery exposure and PET amyloid load variation over 2 years. This finding is in line with a recent study showing the lack of an association between global cortical amyloid deposition and cognitive dysfunction 6 weeks after cardiac surgery <sup>25</sup>.

We also found that the interaction of the exposure to surgery and educational level had a significant effect on the variation of brain metabolism over two years. This result may be explained by the impact of education on pathology and clinical outcomes through cognitive reserve <sup>26</sup>. In our study, participants had on average high educational attainment, indicating a greater cognitive reserve than the general elderly population <sup>27</sup>. Cognitive reserve decreases the risk of developing dementia when cerebral lesions of AD appear <sup>28</sup>. But in contrast, once cognitive changes emerge, those with higher reserve have been shown to have a more rapid decline <sup>29</sup>. This would explain why there is a more rapid decrease in metabolism in higher educated participants with surgery (Supplementary Figure 1).

The link between surgery and changes in brain metabolism is supported by in vitro and animal research, which provides credible evidence that general anaesthesia may precipitate or exacerbate cerebral dysfunction in experimental models of AD. In particular, inhaled anaesthetics have been reported to induce hyperphosphorylation and accumulation of tau protein <sup>30</sup>, the deposition of which is largely correlated to cortical metabolism <sup>31</sup>. In the same way, an inflammatory response induced by surgery seems to be a possible contributor to AD pathogenesis <sup>32</sup>. In animal models, increased inflammation worsens cognition <sup>33</sup> and provokes POCD. And even minor procedures, such as endoscopy , can increase neuro-inflammation. <sup>34</sup>

If postoperative cognitive dysfunctions seem to share, at least in part, the same pathogenic pathways as AD, the mechanisms involved in POCD are multiple, including

neuroinflammation, oxidative stress, impaired dysfunction of autophagic functions, disorders of synaptic and other functions<sup>35</sup>. All these mechanisms are potential targets for preventive or curative therapies<sup>36</sup>. In 2018, expert recommendations were published on perioperative neuroprotection strategies. If no drug treatment had then demonstrated its effectiveness, experts recommend preoperative screening for early cognitive impairment, intraoperative monitoring of sedation and maintenance of blood pressure<sup>37</sup>.

In summary, undergoing surgery is probably an accelerating factor for AD in patients belonging to the preclinical AD continuum, as schemed in Figure 3.

Our study has some limitations. Our sample size is smaller than in some previous studies. However, our participants performed a highly standardized and comprehensive cognitive testing annually, allowing us to demonstrate a persistent decline in executive functions such as mental flexibility and divided attention, which remained significant even after correction for multiple comparison. Our results should still be seen as exploratory findings in need of confirmatory analyses in future studies. Also, loco-regional and sedation anesthesia were quite frequent in our sample. This is due to the fact that the patients were mainly operated on minor surgeries, which ultimately corresponds to the reality of the surgery of the elderly patient, which is above all functional. While this decreases the risk of postoperative delirium, and maybe that of long-term dementia, it does increase the external validity of this study. Interestingly, numerous studies have shown that loco-regional anesthesia does not decrease cognitive risk, compared to general anesthesia. It is likely that the explanation for this comes from the pathophysiology of postoperative cognitive dysfunctions, mainly due to surgical stress that induces neuroinflammation resulting in neuronal impairment or neuronal death<sup>38-40</sup>. The absence of tau marker in our study is another limitation that did not allow us to properly test the association of anaesthesia and surgery with the hallmark biomarkers of AD within the biological framework proposed by the NIA-AA<sup>12</sup>. The possible arrival of disease modifying treatment<sup>41</sup> and of reliable blood-based biomarkers of amyloid and phosphorylated tau<sup>42</sup> will serve both as incentives and enablers of further studies.

As a strength of our study, we also ensured that all surgical events were recorded, firstly by assessing the occurrence of adverse events every six months, secondly by having an anaesthesiologist verify and specify the events of interest for each participant.

In conclusion, high amyloid burden in the brain increases the risk of a subtle POCD (concerning executive functions) after surgery. This impairment may be driven by a decrease in brain metabolism in signature AD regions, especially evidenced in more highly- educated study participants Taken together, our results suggest that a screening test targeting executive

functions should be administered to elderly patients in preoperative anaesthetics consultations, to be able to predict and ultimately prevent POCD.

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## TABLE AND FIGURE

Figure 1: Generalized linear mixed effects models (GLMMs) results on evolution of cognitive scores explained by surgery. No difference was evidenced between the three groups (not operated [none], operated during the first [M0M12] or second [M12M24] year of follow up) in the six cognitive tests.

Figure 2: Impact of amyloid load (evidenced by the three lines: in green mean global amyloid SUVR of 0.6, in blue 1.0 and in red: 1.4) on the longitudinal trajectory of TMT B-A in seconds in participant who were not operated (left box), or operated during the first [M0M12] or second [M12M24] year of follow up, middle and right boxes respectively. What this graph indicates is that there is a subtle executive impairment that appears only in operated participants with moderate to high amyloid loads at baseline.

Figure 3: Schematic representation of the impact of surgery and anaesthesia on cognition in patients at the preclinical stage of AD (A) and of the absence of impact in normal ageing (B). POCD may be an exacerbation of the neurodegenerative processes associated with incipient AD.

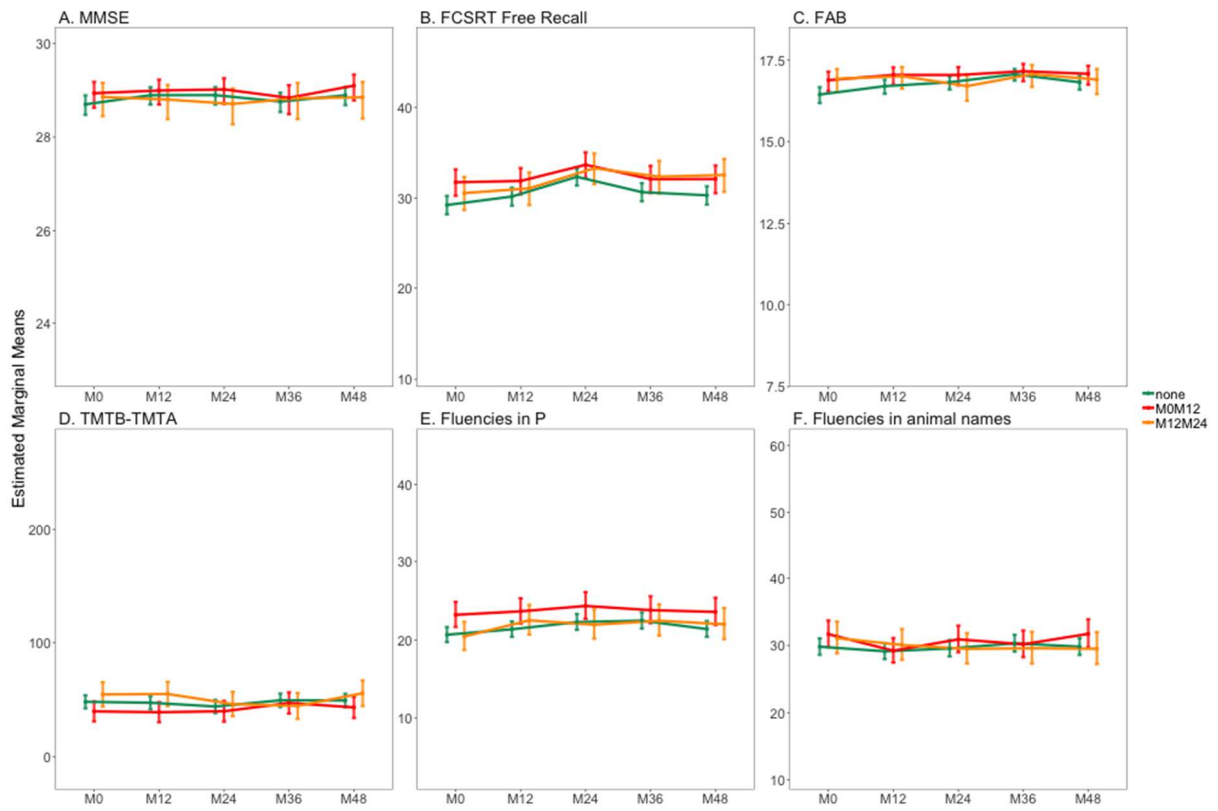


Figure 1

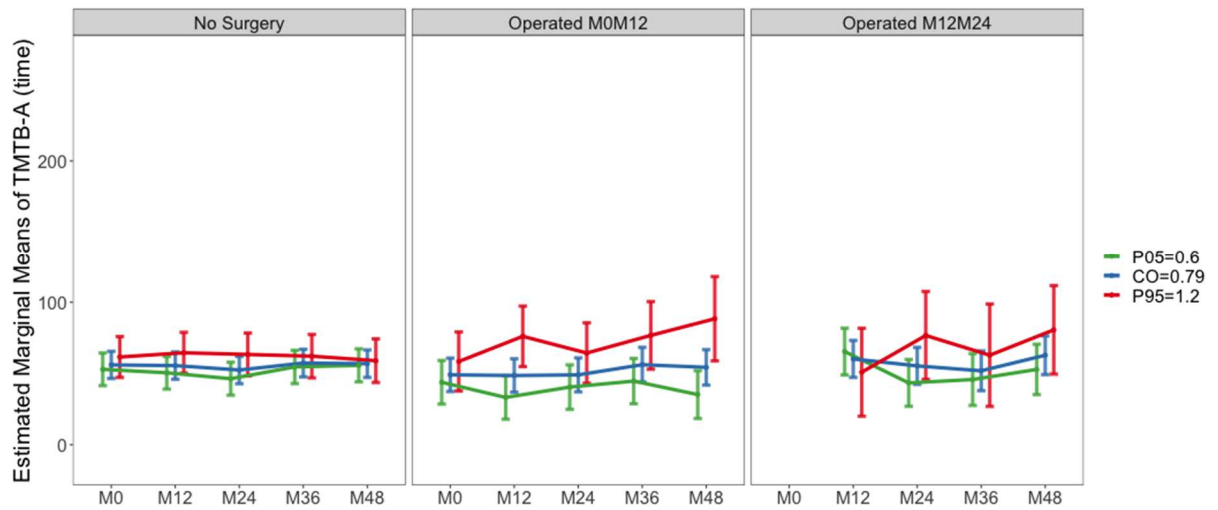


Figure 2



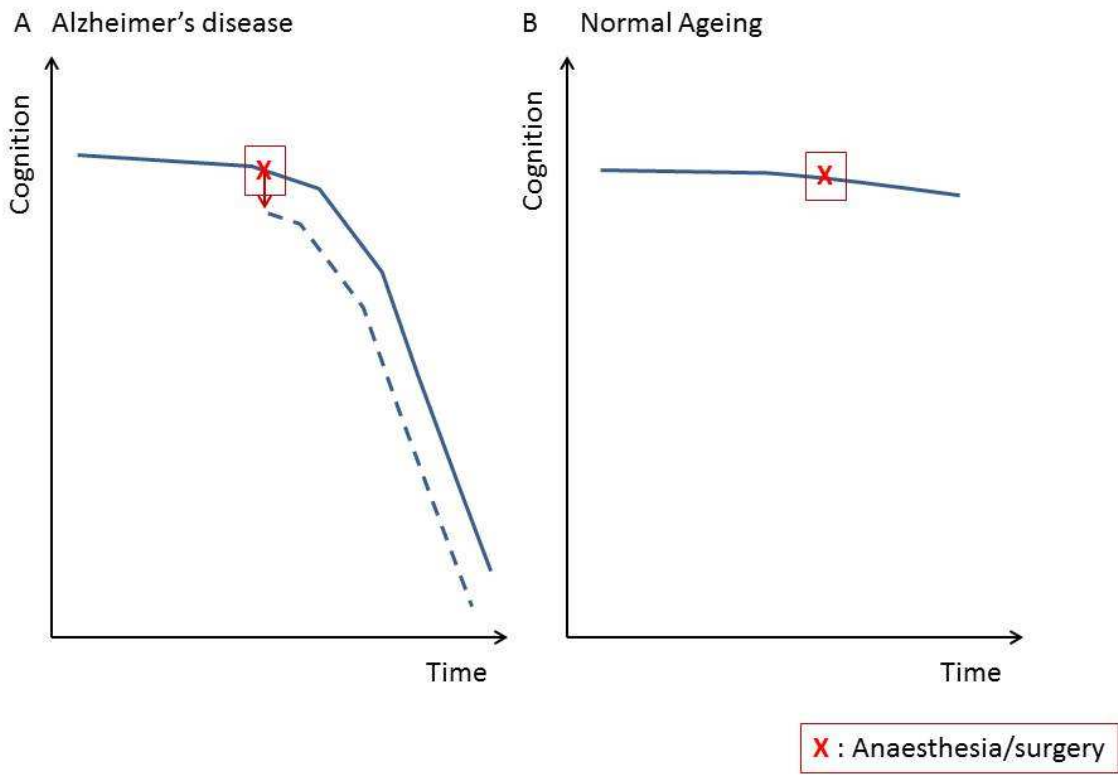


Figure 3