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## Multimorbidity Is Associated with Preclinical Alzheimer's Disease Neuroimaging Biomarkers

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1 **Multimorbidity is associated with preclinical Alzheimer's disease**  
2 **neuroimaging biomarkers**

3

4 **Running Head**

5 **Multimorbidity and cognition in older adults**

6

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44 **Key-words:** Alzheimer's disease, multimorbidity, neuroimaging biomarkers,  
45 amyloid, neurodegeneration.

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51 **Abstract**

52 **Background:** Identifying comorbidities that influence preclinical Alzheimer's  
53 disease (AD) can give some insight about the AD early stages trajectories to  
54 allow new treatment venues and to guide public health systems to prevent  
55 subsequent dementia.

56 **Objective:** To examine the association of multimorbidity with AD  
57 neuroimaging markers in cognitively normal older adults.

58 **Methods:** Cross-sectional design. Data regarding 14 comorbidities were  
59 obtained for all 318 adults aged 70 to 85 years, recruited from the community  
60 to an ongoing prospective monocentric cohort. They underwent standardized  
61 neuropsychological and neuroimaging assessment with automated methods  
62 that measured hippocampal volumes, WMH volumes, FDG-PET SUV in AD  
63 signature regions and amyloid PET SUV ratios. Linear regression was used to  
64 assess the association of multimorbidity with AD neuroimaging biomarkers.

65 **Results:** Multimorbidity is significantly associated to lower hippocampal  
66 volumes ( $-0.03 \pm 0.01$ ;  $P = .012$ ;  $R^2 = .017$ ) and lower FDG-PET SUV ( $-0.027$   
67  $\pm 0.009$ ;  $P = .005$ ;  $R^2 = .022$ ), with no association with amyloid deposition  
68 ( $0.001 \pm 0.007$ ;  $P = .884$ ;  $R^2 = .0001$ ). Taken individually, obesity and  
69 excessive alcohol use are associated with lower FDG-PET values.

70 Surprisingly, obstructive sleep apnea and mood disorders are related to lower  
71 Amyloid-PET SUVr.

72 **Conclusions:** Multimorbidity is associated with preclinical AD imaging  
73 markers of neurodegeneration, but not with amyloid.

74

## 75 **Introduction**

76 Several acquired comorbidities have been described to increase the risk of  
77 developing dementia or Alzheimer's disease (AD).<sup>1</sup> Most of them are  
78 conditions that are modifiable with treatment, such as hypertension,  
79 dyslipidemia or diabetes.<sup>2</sup> The co-occurrence of multiple chronic conditions  
80 ( $\geq 2$  diseases) characterizes multimorbidity, an entity which prevalence rises  
81 with age<sup>3</sup>, affecting more than a half of the older adults population.

82 Multimorbidity has been associated with adverse health outcomes as mild  
83 cognitive impairment,<sup>4</sup> diminished quality of life, functional limitation, frailty  
84 and mortality.<sup>5</sup> Many of these chronic conditions commonly observed in  
85 multimorbidity are also the same established risk factors of AD. Moreover,  
86 they can directly impact brain neurogenesis by different underlying  
87 mechanisms, influencing for example the size of hippocampus towards lower  
88 volumes throughout life.<sup>6</sup>

89 This study aims to examine whether different AD neuroimaging biomarkers of  
90 neurodegeneration and amyloid burden relate to comorbidities individually, as  
91 well as to their accumulation termed "multimorbidity" in cognitively normal  
92 older adults. In the scope of recent failures of targeted drug trials against AD,<sup>7</sup>  
93 the identification of treatable conditions that raise the risk of preclinical AD  
94 might 1) play a role in future trials as enrichment factors at inclusion; 2) give  
95 some mechanistic insight about the early stage of AD to allow new treatment  
96 venues and; 3) guide public health systems to prevent subsequent dementia.

## 97 **Methods**

### 98 **Study population**

99 The INSIGHT-PreAD is an ongoing prospective monocentric cohort with the  
100 objective to determine factors that increase the risk of progression of  
101 cognitively normal older adults to clinical AD. INSIGHT-PreAD enrolled  
102 participants aged 70 to 85 years, with a subjective cognitive decline (SCD)  
103 and no objective cognitive disorders defined by a mini-mental state  
104 examination score (MMSE)  $\geq 27$  and total recall score in the free and cued  
105 selective reminding test (FCSRT)  $\geq 41$ .<sup>8</sup> Exclusion criteria included clinical  
106 dementia rating scale (CDR)  $> 0$ ,<sup>9</sup> visual and auditory functions insufficient for  
107 neuropsychological testing, the existence of a known neurological disease,  
108 recent stroke and illiteracy.

109 The study was approved by the local ethical committee (ANSM 130134B-31)  
110 and all participants signed a written informed consent.

#### 111 **Clinical data**

112 Demographic data were obtained at baseline and a comorbidity profile was  
113 established based on self-reported diagnosis during the standardized clinical  
114 follow-up. The presence of fourteen chronic conditions was assessed:  
115 hypertension, dyslipidemia, diabetes mellitus, atrial fibrillation, heart failure,  
116 chronic kidney disease, obstructive sleep apnea (OSA), active or past  
117 smoking, unhealthy alcohol consumption, prior head trauma, obesity, vitamin  
118 B12 deficiency, depression and post-traumatic stress disorder (PTSD).  
119 Diagnoses were validated by a physician (AM), according to standardized  
120 criteria from the international classification of diseases (ICD-10). Data  
121 regarding chronic kidney failure was not available for 23 subjects.  
122 Regarding mood disorders, we considered the diagnosis present for both  
123 early and late-onset episodes, as well as recurrent disorder. All head trauma

124 episodes were recorded, independent of severity. Excessive alcohol  
125 consumption was defined according to the diagnostic and statistical manual of  
126 mental disorders (DSM-5) criteria.

## 127 **Neuroimaging assessment**

### 128 **Hippocampal volumetry**

129 All participants underwent an MRI at baseline in the same Siemens  
130 Magnetom Verio 3-T scan. The MRI acquisition protocol is described in the  
131 supplementary material.

132 The hippocampal segmentation was performed using a fully automated in-  
133 house developed method, based on simultaneous region deformation driven  
134 by both anatomical and probabilistic priors.<sup>10</sup> Anatomical information was  
135 derived from local anatomical patterns that are stable in controls and AD  
136 patients, around landmarks automatically detected during the deformation.

137 Probabilistic information was derived from an atlas built from the registration  
138 of manually segmented hippocampus from 16 young healthy subjects.

139 Initialization was obtained from global information and deformation is  
140 constrained by local anatomical and probabilistic information.

141 Volumes were normalized by the total intracranial volume (TIV).<sup>11</sup>

### 142 **White Matter Hyperintensities (WMH) volumetry**

143 Automated volumetry of WMH was obtained from all participants using the  
144 WMH Automated Segmentation Algorithm (WHASA) method and expressed  
145 in  $\text{cm}^3$ . WHASA relies on increased contrast between WMH and surrounding  
146 tissues by extracting tissue information from T1 images, registering it to the  
147 FLAIR image and correcting for intensity inhomogeneities.<sup>12</sup> Non-linear  
148 diffusion framework enables then to enhance the contrast of WMH on the

149 FLAIR image and obtain a piecewise constant image.

150 **Positron Emission Tomography studies with 18 Fluoro Deoxyglucose**

151 **(FDG-PET) and with amyloid ligand 18F-Florbetapir**

152 - *FDG-PET and florbetapir images acquisition* - Brain amyloid PET scans

153 were acquired 50 minutes after injection of 370 MBq (10 mCi) of 18F-

154 Florbetapir. Brain FDG-PET scans were obtained 30 minutes after injection of

155 2 MBq/kg of 2-deoxy-2-(18F)fluoro-D-glucose. All acquisitions were performed

156 in a single session on a Philips Gemini GXL scanner and consisted of 3 x 5

157 minutes frames with a voxel size of 2 x 2 x 2 mm<sup>3</sup>. Images were then

158 reconstructed using iterative LOR-RAMLA algorithm. Lastly, frames were

159 realigned, averaged and quality-checked by a dedicated neuroimaging

160 specialist team (CATI for “Centre pour l'Acquisition et le Traitement des

161 Images”, <http://cati-neuroimaging.com/>).

162 - *PET images processing* - The CATI developed a pipeline allowing

163 quantifying radiotracer uptake in the grey matter of untransformed PET

164 images, with high throughput and a step-by-step quality check. The aim was

165 to reduce quantification biases related to spatial normalization, co-registration

166 and partial volume effect (PVE). MRI 3D T1-weighted images were

167 segmented and spatially normalized into the MNI space using the VBM8

168 package implemented in SPM8.<sup>13</sup> Deformation fields, grey and white matter

169 masks were generated and further used to define ROIs. Structural MRI

170 images were co-registered to PET images using SPM8 with visual inspection

171 to detect any co-registration errors. Using inverse deformation fields and

172 matrix transformation, composite cortical ROIs and a reference region were

173 placed in the individual native PET space. After correcting for PVE with the

174 RBV-sGTM method,<sup>14</sup> parametric PET images were created for each  
175 individual, by dividing each voxel with the mean activity extracted from the  
176 reference region.

177 - *PET variables* - Metabolic indexes were calculated in ROIs involving AD  
178 specific regions such as right and left precuneus, posterior cingulate cortex,  
179 associative parietal and temporal cortex, hippocampus, as well as ROIs in the  
180 frontal and occipital cortex.<sup>15</sup> The reference region was the pons. For amyloid  
181 PET images, standard uptake value ratios (SUVR) were calculated by  
182 averaging the mean activity of cortical ROIs: both left and right precuneus,  
183 cingulum posterior, cingulum anterior, parietal, temporal and orbitofrontal  
184 cortex. The reference region was a combination of whole cerebellum and  
185 pons regions.<sup>16</sup>

#### 186 **Statistical analysis**

187 Descriptive data of the population is expressed as number of cases and  
188 proportions for categorical variables and as means and standard deviations  
189 for continuous variables. Differences between men and women were  
190 assessed by Fisher's exact test or t-test if variables were categorical or  
191 continuous, respectively.

192 The associations among the accumulation of comorbidities and their effect as  
193 individual conditions with the AD neuroimaging biomarkers were assessed by  
194 linear regression methods. For this purpose, hippocampal volumes, metabolic  
195 indexes and amyloid-PET SUVR were analyzed as continuous variables in our  
196 models.

197 We predetermined five possible confounding factors for adjustments in the  
198 multivariate analysis: age, sex, educational level, ApoE4 status and WMH

199 volumes. We performed linear regression univariate analysis to evaluate their  
200 association to neuroimaging variables. Variables presenting statistically  
201 significant associations were used as adjustment factors in the multivariate  
202 linear regression model for comorbidity, applied to their respective  
203 neuroimaging biomarker.

204 Results were considered significant at  $P < 0.05$  and all statistical analyses were  
205 performed using SAS software (version 9.4; SAS Institute, Cary).

## 206 **Results**

### 207 **Population characteristics**

208 The cohort of 318 cognitively normal subjects was composed by 204 (64.2%)  
209 women, with a global mean age of 76 years (SD: 3). They have a high mean  
210 sociocultural level (6, SD: 2), on a scale from 1 (no formal education) to 8 (at  
211 least two years post high school graduation). Hypertension, dyslipidemia,  
212 mood disorders and chronic kidney failure were the most common observed  
213 comorbidities and 70% of participants had at least 2 chronic conditions (table  
214 1). Mood disorders were more prevalent in women, whereas hypertension,  
215 heart failure, obstructive sleep apnea and tobacco use were significantly more  
216 prevalent in men. There were no differences regarding APOE4 allele  
217 prevalence.

### 218 **Adjustment factors and neuroimaging biomarkers**

219 Age influenced the 3 biomarkers studied, while female gender was associated  
220 with higher normalized hippocampal volumes and FDG PET, with no  
221 differences in amyloid-PET SUVR (table 2). Higher comorbidity burden  
222 observed in men can partly explain these differences.

223 While ApoE4 status was not associated with FDG-PET indexes, a trend  
224 toward significance was observed in the association of positive ApoE4 status  
225 and lower hippocampal volumes. Interestingly, WMH was not associated with  
226 hippocampal volumes or FDG-PET indexes, however higher WMH volumes  
227 were significantly associated to higher SUVr in amyloid-PET (figure 1).

### 228 **Multimorbidity and neuroimaging biomarkers**

229 The increasing number of comorbidities was significantly associated with  
230 lower hippocampal volumes ( $-0.03 \pm 0.01$ ;  $P = .012$ ;  $R^2 = .017$ ) as well as with  
231 lower SUV ( $-0.027 \pm 0.009$ ;  $P = .005$ ;  $R^2 = .022$ ) in FDG-PET. In the other  
232 hand, we did not observe any association between comorbidities  
233 accumulation and SUVr in amyloid PET ( $0.001 \pm 0.007$ ;  $P = 0.884$ ;  $R^2 = .0001$ ).  
234 After adjustment for possible confounding factors, the association remained  
235 statistically significant only for FDG-PET SUV ( $-0.02 \pm 0.01$ ;  $P = .038$ ;  $R^2 = .07$ ).  
236 Both obesity and excessive alcohol use were associated with lower  
237 metabolism in FDG-PET, in univariate and multivariate models. Moreover,  
238 smoking presented a statically significant association with lower hippocampal  
239 volumes, but no significant association was observed after adjustment for  
240 possible confounding factors (table 3).

241 Increased amyloid-PET SUVr was associated with the presence of  
242 dyslipidemia in the univariate linear regression model ( $0.048 \pm 0.022$ ;  $P = .029$ ;  
243  $R^2 = .047$ ). Surprisingly, OSA and mood disorders were inversely associated  
244 with amyloid-PET SUVr, remaining statistically significant after adjustment for  
245 possible confounding factors (table 3).

### 246 **Discussion**

247 In this study with 318 cognitively normal older adults, we observed that the  
248 accumulation of multiple chronic conditions, i.e. multimorbidity, is associated  
249 with neuroimaging markers of AD neurodegeneration, but not with amyloid  
250 deposition.

251 Some of the multiple chronic conditions explored in our study were singularly  
252 associated to lower hippocampal volumes and lower metabolism in AD-  
253 specific brain regions. The lower metabolism in FDG-PET AD signature  
254 regions was independent of ApoE4 status. These results are in agreement  
255 with a previous study regarding 1449 cognitively normal subjects, in which  
256 investigators observed an association of multimorbidity with FDG-PET  
257 hypometabolism and abnormal AD signature cortical thickness, whereas  
258 these were unrelated to amyloid.<sup>17</sup> Our study demonstrates comparable  
259 results with a different spectrum of comorbidities, adding information  
260 regarding the association with hippocampal atrophy, not yet assessed.

261 Besides that, by using a linear regression statistical approach, we could  
262 establish associations without determining normal/abnormal cut-off values in  
263 neuroimaging variables, showing that the association of comorbidities with  
264 neurodegeneration may be part of a continuum.<sup>18,19</sup> Interactions among  
265 vascular risk factors, frequently observed as comorbidities in older adults are  
266 probably implicated in this pathophysiology.<sup>20,21</sup> Multimorbidity has been  
267 recognized as an entity by itself, exceeding the simple co-existence of  
268 multiple chronic conditions.<sup>22</sup> It has been demonstrated that their interactions  
269 transcend a merely additive effect, presenting a more complex synergism  
270 regarding vascular burden for example, but also other pathophysiological  
271 processes such as inflammation and oxidative stress.<sup>23</sup> Our hypothesis is that

272 different diseases clusters create different illness burden and may impact in a  
273 unique manner neurodegeneration.<sup>24</sup> Therefore, the type, number and  
274 severity of comorbidities may modulate the rate of atrophy and metabolism  
275 decline, being at least one important variable in a complex model of factors  
276 determining the extent of preclinical AD stage.

277 Surprisingly, we did not observe a relation between lower hippocampal  
278 volumes and vascular risk factors, classically related to a negative impact on  
279 hippocampus neurogenesis. This may be explained by our small sample size.

280 We observed that active or past smoking was associated with lower  
281 hippocampal volumes. It has been demonstrated that chronic cigarette  
282 smoking may negatively impact cognition, including memory, due to oxidative  
283 stress-induced lesions.<sup>25</sup> We found that a chronic excessive alcohol use was  
284 associated with lower metabolism in FDG-PET. Alcohol consumption seems  
285 to influence hippocampal neurogenesis as well as brain metabolism.<sup>26</sup>

286 Intoxication states are associated with a switch in metabolism patterns,  
287 increasing acetate metabolism and reducing glucose use, as it was  
288 demonstrated in FDG-PET studies.<sup>27</sup> It is not clear whether these effects may  
289 be transitory or permanent in the path towards neurodegeneration.

290 In this study, obesity was related to lower metabolism in FDG-PET, but not to  
291 hippocampal atrophy. Obesity seems to be implicated in neurodegeneration,  
292 increasing the risk of cognitive impairment in late life and has been shown to  
293 be associated with decreased brain volumes.<sup>28,29</sup>

294 In this study, OSA and mood disorders were associated with lower amyloid-  
295 PET SUVR. However, there is evidence that both comorbidities may be  
296 actually associated with increased amyloid deposition. OSA leads to recurrent

297 sleep fragmentation and hypoxia, which upregulates the expression of the  
298 amyloid precursor protein (APP), diminishing A $\beta$  clearance from the brain.<sup>30</sup> In  
299 animal models, chronic hypoxia enhanced amyloid plaques generation with a  
300 significant decline in memory.<sup>31</sup> Depression is not only an AD risk factor, but it  
301 can also be an initial phenotype of AD.<sup>32</sup> There is evidence relating mood  
302 disorders to amyloid deposition, mainly from cross-sectional studies, showing  
303 that subjects with major depression have lower CSF AB42 and higher amyloid  
304 deposition in PET studies.<sup>33,34</sup> The discrepancies with our data may be a  
305 result of the lack of information available regarding the depression episode  
306 (early-life, late-late or recurrent), as well as the severity of the disease and  
307 possible treatments implemented for both comorbidities.

308 As recent data from previous cross-sectional studies, we also found an  
309 association between higher WMH volumes and amyloid deposition.<sup>35</sup> WMH  
310 are highly prevalent and clearly related to vascular risk factors in older adults,  
311 however the possible causal relationship between amyloid and WMH needs  
312 further exploration in longitudinal studies. WMH could accelerate amyloid  
313 deposition, but amyloid may also affect WMH burden, independently of  
314 vascular risk factors treatment.

315 This study has strengths, but also some limitations. The cross-sectional  
316 analyses do not allow us to infer temporality associations between  
317 comorbidities and neuroimaging biomarkers. Also, there is a possible  
318 selection bias regarding the participants of INSIGHT PreAD who are mostly  
319 highly educated. This could influence the prevalence of comorbidities.

320 The main strength of this study lies in its standardized multimodal clinical and  
321 neuroimaging acquisition protocols and its monocentric nature, allowing for

322 optimal homogeneity of the cohort. A future longitudinal analysis in  
323 multimorbidity may help to understand the progression of neurodegeneration  
324 and amyloid deposition along with possible causality associations. Various  
325 comorbidities may be targeted with adequate treatment, raising the question  
326 of how their multimodal assessment and therapies during the early and late  
327 adult lifespan could impact pre-clinical AD trajectories.

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330 This study was sponsored by Pfizer, Avid, the Foundation Plan Alzheimer and  
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341 Anne Bertrand reports no disclosures.

342

343 **Author contributions:**

344 Aline Mendes – takes full responsibility for the data. Contribution to the study  
345 concept and design, data acquisition, analysis, interpretation and manuscript  
346 elaboration

347 Stéphane Epelbaum - study supervision (concept and design), interpretation  
348 and critical revision of the manuscript

349 Marie-Odile Habert – PET data acquisition and analysis, critical revision of the  
350 manuscript

351 Hugo Bertin - PET data acquisition and analysis

352 Sophie Tezenas du Montcel – data analysis

353 Marcel Levy - subjects' follow up, critical revision of the manuscript

354 Bruno Dubois – Interpretation and critical revision of the manuscript

355 Anne Bertrand – MRI data acquisition and analysis

356

357 **References**

- 358 1. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for  
359 primary prevention of Alzheimer's disease: an analysis of population-  
360 based data. *Lancet Neurol.* 2014;13:788–794.
- 361 2. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife  
362 cardiovascular risk factors and risk of dementia in late life. *Neurology.*  
363 2005;64:277–281.
- 364 3. Marengoni A, Rizzuto D, Wang H-X, Winblad B, Fratiglioni L. Patterns of  
365 chronic multimorbidity in the elderly population. *J. Am. Geriatr. Soc.*  
366 2009;57:225–230.
- 367 4. Vassilaki M, Aakre JA, Cha RH, Kremers WK, St Sauver JL, Mielke MM,  
368 et al. Multimorbidity and Risk of Mild Cognitive Impairment. *J. Am. Geriatr.*  
369 *Soc.* 2015;63:1783–1790.
- 370 5. Smith SM, Wallace E, O'Dowd T, Fortin M. Interventions for improving  
371 outcomes in patients with multimorbidity in primary care and community  
372 settings. *Cochrane Database Syst. Rev.* 2016;3:CD006560.
- 373 6. Fotuhi M, Do D, Jack C. Modifiable factors that alter the size of the  
374 hippocampus with ageing. *Nat. Rev. Neurol.* 2012;8:189–202.

- 375 7. Doody RS, Thomas RG, Farlow M, Iwatsubo T, Vellas B, Joffe S, et al.  
376 Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease.  
377 N. Engl. J. Med. 2014;370:311–321.
- 378 8. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical  
379 method for grading the cognitive state of patients for the clinician. J.  
380 Psychiatr. Res. 1975;12:189–198.
- 381 9. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical  
382 scale for the staging of dementia. Br. J. Psychiatry J. Ment. Sci.  
383 1982;140:566–572.
- 384 10. Chupin M, Gerardin E, Cuingnet R, Boutet C, Lemieux L, Lehericy S, et  
385 al. Fully automatic hippocampus segmentation and classification in  
386 Alzheimer's disease and mild cognitive impairment applied on data from  
387 ADNI. Hippocampus. 2009;19:579–587.
- 388 11. Colliot O, Chetelat G, Chupin M, Desgranges B, Magnin B, Benali H, et al.  
389 Discrimination between Alzheimer disease, mild cognitive impairment,  
390 and normal aging by using automated segmentation of the hippocampus.  
391 Radiology. 2008;248:194–201.
- 392 12. Samaille T, Fillon L, Cuingnet R, Jouvent E, Chabriat H, Dormont D, et al.  
393 Contrast-based fully automatic segmentation of white matter  
394 hyperintensities: method and validation. PloS One. 2012;7:e48953.
- 395 13. VBM at Structural Brain Mapping Group [Internet]. [cited 2017 Jan  
396 7]; Available from: <http://dbm.neuro.uni-jena.de/vbm/>

- 397 14. Thomas BA, Erlandsson K, Modat M, Thurfjell L, Vandenberghe R,  
398 Ourselin S, et al. The importance of appropriate partial volume correction  
399 for PET quantification in Alzheimer's disease. *Eur. J. Nucl. Med. Mol.*  
400 *Imaging.* 2011;38:1104–1119.
- 401 15. Jack CRJ, Knopman DS, Weigand SD, Wiste HJ, Vemuri P, Lowe V, et  
402 al. An operational approach to National Institute on Aging-Alzheimer's  
403 Association criteria for preclinical Alzheimer disease. *Ann. Neurol.*  
404 2012;71:765–775.
- 405 16. Brendel M, Hogenauer M, Delker A, Sauerbeck J, Bartenstein P, Seibyl J,  
406 et al. Improved longitudinal [(18)F]-AV45 amyloid PET by white matter  
407 reference and VOI-based partial volume effect correction. *NeuroImage.*  
408 2015;108:450–459.
- 409 17. Vassilaki M, Aakre JA, Mielke MM, Geda YE, Kremers WK, Alhurani RE,  
410 et al. Multimorbidity and neuroimaging biomarkers among cognitively  
411 normal persons. *Neurology.* 2016;86:2077–2084.
- 412 18. Roberts RO, Knopman DS, Cha RH, Mielke MM, Pankratz VS, Boeve BF,  
413 et al. Diabetes and elevated hemoglobin A1c levels are associated with  
414 brain hypometabolism but not amyloid accumulation. *J. Nucl. Med. Off.*  
415 *Publ. Soc. Nucl. Med.* 2014;55:759–764.
- 416 19. Yaffe K, Kanaya A, Lindquist K, Simonsick EM, Harris T, Shorr RI, et al.  
417 The metabolic syndrome, inflammation, and risk of cognitive decline.  
418 *JAMA.* 2004;292:2237–2242.

- 419 20. Bangen KJ, Nation DA, Delano-Wood L, Weissberger GH, Hansen LA,  
420 Galasko DR, et al. Aggregate effects of vascular risk factors on  
421 cerebrovascular changes in autopsy-confirmed Alzheimer's disease.  
422 *Alzheimers Dement. J. Alzheimers Assoc.* 2015;11:394–403.e1.
- 423 21. Wiseman RM, Saxby BK, Burton EJ, Barber R, Ford GA, O'Brien JT.  
424 Hippocampal atrophy, whole brain volume, and white matter lesions in  
425 older hypertensive subjects. *Neurology.* 2004;63:1892–1897.
- 426 22. Fabbri E, Zoli M, Gonzalez-Freire M, Salive ME, Studenski SA, Ferrucci  
427 L. Aging and Multimorbidity: New Tasks, Priorities, and Frontiers for  
428 Integrated Gerontological and Clinical Research. *J. Am. Med. Dir. Assoc.*  
429 2015;16:640–647.
- 430 23. Marengoni A, Angleman S, Melis R, Mangialasche F, Karp A, Garmen A,  
431 et al. Aging with multimorbidity: a systematic review of the literature.  
432 *Ageing Res. Rev.* 2011;10:430–439.
- 433 24. Hsu H-C. Trajectories of multimorbidity and impacts on successful aging.  
434 *Exp. Gerontol.* 2015;66:32–38.
- 435 25. Gazdzinski S, Durazzo TC, Yeh P-H, Hardin D, Banys P, Meyerhoff DJ.  
436 Chronic cigarette smoking modulates injury and short-term recovery of  
437 the medial temporal lobe in alcoholics. *Psychiatry Res.* 2008;162:133–  
438 145.
- 439 26. Lee J, Im S-J, Lee S-G, Stadlin A, Son J-W, Shin C-J, et al. Volume of  
440 hippocampal subfields in patients with alcohol dependence. *Psychiatry*  
441 *Res.* 2016;258:16–22.

- 442 27. Volkow ND, Wang G-J, Shokri Kojori E, Fowler JS, Benveniste H,  
443 Tomasi D. Alcohol decreases baseline brain glucose metabolism more in  
444 heavy drinkers than controls but has no effect on stimulation-induced  
445 metabolic increases. *J. Neurosci. Off. J. Soc. Neurosci.* 2015;35:3248–  
446 3255.
- 447 28. Whitmer RA, Gustafson DR, Barrett-Connor E, Haan MN, Gunderson EP,  
448 Yaffe K. Central obesity and increased risk of dementia more than three  
449 decades later. *Neurology.* 2008;71:1057–1064.
- 450 29. Albanese E, Davis B, Jonsson PV, Chang M, Aspelund T, Garcia M, et al.  
451 Overweight and Obesity in Midlife and Brain Structure and Dementia 26  
452 Years Later: The AGES-Reykjavik Study. *Am. J. Epidemiol.*  
453 2015;181:672–679.
- 454 30. Austin BP, Nair VA, Meier TB, Xu G, Rowley HA, Carlsson CM, et al.  
455 Effects of hypoperfusion in Alzheimer's disease. *J. Alzheimers Dis. JAD.*  
456 2011;26 Suppl 3:123–133.
- 457 31. Guglielmotto M, Aragno M, Autelli R, Giliberto L, Novo E, Colombatto S,  
458 et al. The up-regulation of BACE1 mediated by hypoxia and ischemic  
459 injury: role of oxidative stress and HIF1alpha. *J. Neurochem.*  
460 2009;108:1045–1056.
- 461 32. Dotson VM, Davatzikos C, Kraut MA, Resnick SM. Depressive symptoms  
462 and brain volumes in older adults: a longitudinal magnetic resonance  
463 imaging study. *J. Psychiatry Neurosci. JPN.* 2009;34:367–375.

- 464 33. Pomara N, Bruno D, Osorio RS, Reichert C, Nierenberg J, Sarreal AS, et  
465 al. State-dependent alterations in cerebrospinal fluid Abeta42 levels in  
466 cognitively intact elderly with late-life major depression. *Neuroreport*.  
467 2016;27:1068–1071.
- 468 34. Wu K-Y, Hsiao I-T, Chen C-S, Chen C-H, Hsieh C-J, Wai Y-Y, et al.  
469 Increased brain amyloid deposition in patients with a lifetime history of  
470 major depression: evidenced on 18F-florbetapir (AV-45/Amyvid) positron  
471 emission tomography. *Eur. J. Nucl. Med. Mol. Imaging*. 2014;41:714–722.
- 472 35. Scott JA, Braskie MN, Tosun D, Maillard P, Thompson PM, Weiner M, et  
473 al. Cerebral amyloid is associated with greater white-matter  
474 hyperintensity accrual in cognitively normal older adults. *Neurobiol. Aging*.  
475 2016;48:48–52.
- 476

477 Table 1. Characteristics of the study population at baseline.

478

Characteristics	Women n=204	Men n=114	p value	Total n=318
Age, mean (SD)	76.0 (3.3)	76.2 (3.9)	0.654	76.1 (3.5)
Education level, mean (SD)	5.9 (2.0)	6.7 (2.0)	0.001	6.2 (2.1)
APOE4, n (%)	41 (20.1)	18 (15.8)	0.371	59 (18.6)
HTA, n (%)	77 (37.8)	60 (52.6)	0.013	137 (43.1)
Atrial Fibrillation, n (%)	18 (8.8)	11 (9.6)	0.84	29 (9.1)
Heart Failure, n (%)	17 (8.3)	19 (16.7)	0.028	36 (11.3)
Dyslipidemia, n (%)	82 (40.2)	54 (47.4)	0.238	136 (42.8)
Diabetes, n (%)	10 (4.9)	6 (5.3)	>0.99	16 (5)
Obstructive sleep apnea, n (%)	7 (3.4)	13 (11.4)	0.007	20 (6.3)
Head trauma, n (%)	20 (9.8)	6 (5.3)	0.201	26 (8.2)
Mood disorders, n (%)	71 (34.8)	17 (14.9)	<0.0001	88 (27.7)
B12 deficiency, n (%)	3 (1.5)	2 (1.8)	>0.99	5 (1.6)
PTSD, n (%)	0	1 (0.9)	0.358	1 (0.3)
Unhealthy alcohol use, n (%)	17 (8.3)	14 (12.3)	0.324	31 (9.7)
Smoked ever, n (%)	55 (27)	69 (60.5)	<0.0001	124 (39)
Current smoking, n (%)	12 (5.9)	9 (7.9)	0.489	21 (6.6)
BMI, mean (SD)	25.0 (3.8)	25.5 (2.9)	0.236	25.2 (3.5)
Obesity, n (%)	20 (9.8)	6 (5.3)	0.201	26 (8.2)
Chronic kidney disease, n (%)	41 (21.7)	23 (21.7)	>0.99	64 (21.7)
Comorbidities total, mean (SD)	2.2 (1.4)	2.7 (1.5)	0.004	2.4 (1.5)
Number of comorbidities, n (%)			0.011	
0-1	71 (34.8)	24 (21.1)		95 (29.9)
≥2	133 (65.2)	90 (78.9)		223 (70.1)

479

480 Abbreviations: HTA = Arterial hypertension; PTSD = Post-traumatic stress

481 disorder; BMI = Body mass index.

482 Fisher's exact test categorical variables or t-test for continuous variables.

483 Level of education is assessed by a scale from 1 (no formal education) to 8

484 (at least two years post high school graduation).

485

486 Table 2. Assessment of the association of potential adjustment factors for the  
 487 multivariate comorbidity model with AD neuroimaging biomarkers.

488

Adjustment factors	Hippocampal volume	<i>P</i> value	FDG-PET SUV	<i>P</i> value	Amyloid-PET SUVr	<i>P</i> value
	n=318		n=314		n=318	
<b>Age</b>	-0.023 ±0.005	<.001	-0.01 ±0.004	0.013	0.006 ±0.003	0.043
<b>Women</b>	0.169 ±0.035	<.001	0.112 ±0.03	<.001	-0.026 ±0.022	0.235
<b>Level of education</b>	0.001 ±0.008	0.927	-0.012 ±0.007	0.073	-0.001 ±0.005	0.793
<b>APOE4 status</b>	-0.081 ±0.042	0.053	-0.007 ±0.036	0.837	0.123 ±0.026	<.001
<b>WMH volume</b>	-0.002 ±0.001	0.2	0.001 ±0.001	0.365	0.003 ±0.001	0.0002

489

490 Abbreviations: WMH = white matter hyperintensities.

491 Linear regression univariate analysis.

492 Level of education is assessed by a scale from 1 (no formal education) to 8

493 (at least two years post high school graduation).

494 Table 3. Associations of multimorbidity and comorbidities individually with AD  
 495 neuroimaging biomarkers.

496

	Hippocampal volume	FDG-PET SUV	Amyloid-PET SUVr
	<b>n=318</b>	<b>n=314</b>	<b>n=318</b>
<b>Comorbidity number</b>	-0.03 ±0.01	-0.027 ±0.009	0.001 ±0.007
	<i>P</i> =0.012	<i>P</i> =0.005	<i>P</i> =0.884
	<i>R</i> <sup>2</sup> =0.017	<i>R</i> <sup>2</sup> =0.022	<i>R</i> <sup>2</sup> =0.0001
<b>Adjustment factors</b>	<b>Age, Sex, APOE4 status</b>	<b>Age, Sex</b>	<b>ApoE4, Age, WMH</b>
<b>Comorbidity number after adjustment</b>	-0.017 ±0.01	-0.02 ±0.01	0.0004 ±0.007
	<i>P</i> =0.125	<i>P</i> =0.038	<i>P</i> =0.96
	<i>R</i> <sup>2</sup> =0.17	<i>R</i> <sup>2</sup> =0.07	<i>R</i> <sup>2</sup> =0.122
<b>Comorbidities individually</b>	<b>n=295</b>	<b>n=292</b>	<b>n=295</b>
	<b>Tobacco use</b>	<b>Obesity</b>	<b>Obstructive Sleep Apnea</b>
	-0.081 ±0.035	-0.108 ±0.051	-0.095 ±0.043
	<i>P</i> =0.022	<i>P</i> =0.037	<i>P</i> =0.028
	<i>R</i> <sup>2</sup> =0.018	<i>R</i> <sup>2</sup> =0.041	<i>R</i> <sup>2</sup> =0.016
		<b>Excessive alcohol use</b>	<b>Mood disorders</b>
		-0.138 ±0.049	-0.051 ±0.024
		<i>P</i> =0.005	<i>P</i> =0.035
		<i>R</i> <sup>2</sup> =0.027	<i>R</i> <sup>2</sup> =0.031
			<b>Dyslipidemia</b>
			0.048 ±0.022
			<i>P</i> =0.029
			<i>R</i> <sup>2</sup> =0.047
<b>Adjustment factors</b>	<b>Age, Sex, APOE4 status</b>	<b>Age, Sex</b>	<b>Age, APOE4 status, WMH</b>
<b>Comorbidities individually after adjustments</b>	<b>Tobacco use</b>	<b>Obesity</b>	<b>Obstructive Sleep Apnea</b>
	-0.059 ±0.035	-0.142 ±0.05	-0.084 ±0.04
	<i>P</i> =0.094	<i>P</i> =0.005	<i>P</i> =0.039
	<i>R</i> <sup>2</sup> =0.169		
		<b>Excessive alcohol use</b>	<b>Mood disorders</b>
		-0.112 ±0.045	-0.053 ±0.022
		<i>P</i> =0.014	<i>P</i> =0.018
		<i>R</i> <sup>2</sup> =0.094	
			<b>Dyslipidemia</b>
			0.022 ±0.02
			<i>P</i> =0.29
			<i>R</i> <sup>2</sup> =0.148

497 Linear regression models in univariate and multivariate analysis; results  
498 expressed as *Parameter Estimate ±Standard Error*. As for the adjustment  
499 factors, significant associations in univariate analysis realized for 5 pre-  
500 determined factors (age, sex, educational level, ApoE4 status and WMH  
501 volumes) were incorporated in each model of AD neuroimaging biomarker.  
502 Individual comorbidities not shown in the table did not have a statistically  
503 significant association ( $P<0.05$ ) in the univariate model. Abbreviations: WMH  
504 = White matter hyperintensities.  
505

506 Figure 1. Association of WMH volumes with amyloid-PET SUVR.

507

508 <sup>a</sup> Linear regression model,  $0.003 \pm 0.0008$ ;  $P < 0.001$ ;  $R^2 = 0.12$ .

509 <sup>b</sup> The association remains statistically significant after exclusion of this outlier  
510 participant from the analysis.

511 Abbreviations: WMH = White matter hyperintensities.