

Multimorbidity Is Associated with Preclinical Alzheimer's Disease Neuroimaging Biomarkers

Aline Mendes, Sophie Tézenas Du Montcel, Marcel Levy, Anne Bertrand, Marie-Odile Habert, Hugo Bertin, Bruno Dubois, Stéphane Epelbaum

► **To cite this version:**

Aline Mendes, Sophie Tézenas Du Montcel, Marcel Levy, Anne Bertrand, Marie-Odile Habert, et al.. Multimorbidity Is Associated with Preclinical Alzheimer's Disease Neuroimaging Biomarkers. *Dementia and Geriatric Cognitive Disorders*, Karger, 2018, 45 (5-6), pp.272-281. 10.1159/000489007 . hal-01958870

HAL Id: hal-01958870

<https://hal.sorbonne-universite.fr/hal-01958870>

Submitted on 19 Dec 2018

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

3

4 **Running Head**

5 **Multimorbidity and cognition in older adults**

6

7 Aline Mendes^{1, 2}, MD, Sophie Tezenas du Montcel^{3, 4}, MD, PhD, Marcel Levy²
8 MD, Anne Bertrand MD^{5,6,7}, PhD, Marie Odile Habert MD⁸, Hugo Bertin⁸,
9 Bruno Dubois MD², Stéphane Epelbaum^{2,5,7} MD, PhD.

10

11 INSIGHT-PreAD study group

12 ¹ Department of internal medicine, rehabilitation and geriatrics

13 Geneva University Hospitals, Switzerland.

14 ² Institut de la mémoire et de la maladie d'Alzheimer, Département de
15 neurologie, Hôpital de la Pitié Salpêtrière, 47 Bd de l'Hôpital, 75013, Paris,
16 France.

17 ³ Sorbonne Universités, Université Pierre et Marie Curie (UPMC) Univ Paris
18 06, UMR S 1136, INSERM U 1136, Institut Pierre Louis d'Epidémiologie et de
19 Santé Publique, F-75013, Paris, France.

20 ⁴ AP-HP, Biostatistics Unit, Groupe Hospitalier Pitié-Salpêtrière, F-75013,
21 Paris, France.

22 ⁵ Sorbonne Universités, UPMC Univ Paris 06, Inserm, CNRS, Institut du
23 cerveau et la moelle (ICM), AP-HP - Hôpital Pitié-Salpêtrière, Boulevard de
24 l'hôpital, F-75013, Paris, France.

25

26 ⁶ AP-HP, Hôpital de la Pitié-Salpêtrière, Department of Neuroradiology, F-
27 75013, Paris, France

28 ⁷ Inria Paris, Aramis project-team, 75013, Paris, France.

29 ⁸ Nuclear Medicine Department, University Hospital Pitié Salpêtrière, 75013
30 Paris, France.

31 Title character count: 89

32 Number of references: 35

33 Number of tables: 3

34 Number of figures: 1

35 Word count abstract: 200

36 Word count paper: 2396

37

38 **Corresponding author:** Aline Mendes, aline.mendes@hcuge.ch

39 Geneva University Hospitals

40 Departement of Internal Medicine, Rehabilitation and Geriatrics

41 Chemin du Pont-Bochet 3, 1226 Thônex

42 tel: +41 793144344

43

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

46

47

48

49

50

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 ± 0.01 ; $P = .012$; $R^2 = .017$) and lower FDG-PET SUV (-0.027
67 ± 0.009 ; $P = .005$; $R^2 = .022$), with no association with amyloid deposition
68 (0.001 ± 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).¹ Most of them are
78 conditions that are modifiable with treatment, such as hypertension,
79 dyslipidemia or diabetes.² The co-occurrence of multiple chronic conditions
80 (≥ 2 diseases) characterizes multimorbidity, an entity which prevalence rises
81 with age³, affecting more than a half of the older adults population.

82 Multimorbidity has been associated with adverse health outcomes as mild
83 cognitive impairment,⁴ diminished quality of life, functional limitation, frailty
84 and mortality.⁵ 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.⁶

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,⁷
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) ≥ 27 and total recall score in the free and cued
105 selective reminding test (FCSRT) ≥ 41 .⁸ Exclusion criteria included clinical
106 dementia rating scale (CDR) > 0 ,⁹ 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.¹⁰ 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).¹¹

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 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.¹² 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 mm³. 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 SPM8.¹³ 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,¹⁴ 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.¹⁵ 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.¹⁶

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 ± 0.01 ; $P = .012$; $R^2 = .017$) as well as with
231 lower SUV (-0.027 ± 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 ± 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 ± 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 ± 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.¹⁷ 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.^{18,19} Interactions among
265 vascular risk factors, frequently observed as comorbidities in older adults are
266 probably implicated in this pathophysiology.^{20,21} Multimorbidity has been
267 recognized as an entity by itself, exceeding the simple co-existence of
268 multiple chronic conditions.²² 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.²³ Our hypothesis is that

272 different diseases clusters create different illness burden and may impact in a
273 unique manner neurodegeneration.²⁴ 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.²⁵ 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.²⁶

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.²⁷ 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.^{28,29}

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 β clearance from the brain.³⁰ In
299 animal models, chronic hypoxia enhanced amyloid plaques generation with a
300 significant decline in memory.³¹ Depression is not only an AD risk factor, but it
301 can also be an initial phenotype of AD.³² 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.^{33,34} 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.³⁵ 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.

328 **Acknowledgements**

329 **Conflict of Interest:**

330 This study was sponsored by Pfizer, Avid, the Foundation Plan Alzheimer and
331 the IHU-A-ICM.

332 Aline Mendes reports no disclosures.

333 Sophie Tezenas du Montcel reports no disclosures.

334 Marcel Levy reports no disclosures.

335 Marie-Odile Habert has received honoraria as a speaker or consultant for
336 AVID-LILLY, GE Healthcare, and PIRAMAL companies.

337 Stéphane Epelbaum has received honoraria as a speaker or consultant for
338 ELI-LILLY and GE Healthcare.

339 Bruno Dubois has received honoraria as a speaker or consultant for ELI-
340 LILLY and GE Healthcare.

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	
Age	-0.023 ±0.005	<.001	-0.01 ±0.004	0.013	0.006 ±0.003	0.043
Women	0.169 ±0.035	<.001	0.112 ±0.03	<.001	-0.026 ±0.022	0.235
Level of education	0.001 ±0.008	0.927	-0.012 ±0.007	0.073	-0.001 ±0.005	0.793
APOE4 status	-0.081 ±0.042	0.053	-0.007 ±0.036	0.837	0.123 ±0.026	<.001
WMH volume	-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
	n=318	n=314	n=318
Comorbidity number	-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> ² =0.017	<i>R</i> ² =0.022	<i>R</i> ² =0.0001
Adjustment factors	Age, Sex, APOE4 status	Age, Sex	ApoE4, Age, WMH
Comorbidity number after adjustment	-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> ² =0.17	<i>R</i> ² =0.07	<i>R</i> ² =0.122
Comorbidities individually	n=295	n=292	n=295
	Tobacco use	Obesity	Obstructive Sleep Apnea
	-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> ² =0.018	<i>R</i> ² =0.041	<i>R</i> ² =0.016
		Excessive alcohol use	Mood disorders
		-0.138 ±0.049	-0.051 ±0.024
		<i>P</i> =0.005	<i>P</i> =0.035
		<i>R</i> ² =0.027	<i>R</i> ² =0.031
			Dyslipidemia
			0.048 ±0.022
			<i>P</i> =0.029
			<i>R</i> ² =0.047
Adjustment factors	Age, Sex, APOE4 status	Age, Sex	Age, APOE4 status, WMH
Comorbidities individually after adjustments	Tobacco use	Obesity	Obstructive Sleep Apnea
	-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> ² =0.169		
		Excessive alcohol use	Mood disorders
		-0.112 ±0.045	-0.053 ±0.022
		<i>P</i> =0.014	<i>P</i> =0.018
		<i>R</i> ² =0.094	
			Dyslipidemia
			0.022 ±0.02
			<i>P</i> =0.29
			<i>R</i> ² =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 ^a Linear regression model, 0.003 ± 0.0008 ; $P < 0.001$; $R^2 = 0.12$.

509 ^b The association remains statistically significant after exclusion of this outlier
510 participant from the analysis.

511 Abbreviations: WMH = White matter hyperintensities.