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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, 2018, 45 (5-6), pp.272-281. 10.1159/000489007 . hal-01958870

HAL Id: hal-01958870

https://hal.sorbonne-universite.fr/hal-01958870v1

Submitted on 19 Dec 2018

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Multimorbidity is associated with preclinical Alzheimer's disease neuroimaging biomarkers

Running Head

Multimorbidity and cognition in older adults

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Title character count: 89

Number of references: 35

Number of tables: 3

Number of figures: 1

Word count abstract: 200

Word count paper: 2396

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

Abstract

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

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

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

Results: Multimorbidity is significantly associated to lower hippocampal volumes (-0.03 ±0.01; P = .012; R2 = .017) and lower FDG-PET SUV (-0.027 ±0.009; P = .005; R2 = .022), with no association with amyloid deposition (0.001 ±0.007; P = .884; R2 = .0001). Taken individually, obesity and excessive alcohol use are associated with lower FDG-PET values. Surprisingly, obstructive sleep apnea and mood disorders are related to lower Amyloid-PET SUVr.

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

Introduction

Several acquired comorbidities have been described to increase the risk of developing dementia or Alzheimer's disease (AD).[1] Most of them are conditions that are modifiable with treatment, such as hypertension, dyslipidemia or diabetes.[2] The co-occurrence of multiple chronic conditions (≥2 diseases) characterizes multimorbidity, an entity which prevalence rises with age[3], affecting more than a half of the older adults population. Multimorbidity has been associated with adverse health outcomes as mild cognitive impairment,[4] diminished quality of life, functional limitation, frailty and mortality.[5] Many of these chronic conditions commonly observed in multimorbidity are also the same established risk factors of AD. Moreover, they can directly impact brain neurogenesis by different underlying mechanisms, influencing for example the size of hippocampus towards lower volumes throughout life. [6]

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

Methods

Study population

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

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

Clinical data

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

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

Neuroimaging assessment

Hippocampal volumetry

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

The hippocampal segmentation was performed using a fully automated in-house developed method, based on simultaneous region deformation driven by both anatomical and probabilistic priors.[10] Anatomical information was derived from local anatomical patterns that are stable in controls and AD patients, around landmarks automatically detected during the deformation. Probabilistic information was derived from an atlas built from the registration of manually segmented hippocampus from 16 young healthy subjects. Initialization was obtained from global information and deformation is constrained by local anatomical and probabilistic information.

Volumes were normalized by the total intracranial volume (TIV).[11]

White Matter Hyperintensities (WMH) volumetry

Automated volumetry of WMH was obtained from all participants using the WMH Automated Segmentation Algorithm (WHASA) method and expressed in cm^3. WHASA relies on increased contrast between WMH and surrounding tissues by extracting tissue information from T1 images, registering it to the FLAIR image and correcting for intensity inhomogeneities.[12] Non-linear diffusion framework enables then to enhance the contrast of WMH on the

FLAIR image and obtain a piecewise constant image.

Positron Emission Tomography studies with 18 Fluoro Deoxyglucose (FDG-PET) and with amyloid ligand 18F-Florbetapir

- *FDG-PET and florbetapir images acquisition* - Brain amyloid PET scans were acquired 50 minutes after injection of 370 MBq (10 mCi) of 18F-Florbetapir. Brain FDG-PET scans were obtained 30 minutes after injection of 2 MBq/kg of 2-deoxy-2-(18F)fluoro-D-glucose. All acquisitions were performed in a single session on a Philips Gemini GXL scanner and consisted of 3 x 5 minutes frames with a voxel size of 2 x 2 x 2 mm^3. Images were then reconstructed using iterative LOR-RAMLA algorithm. Lastly, frames were realigned, averaged and quality-checked by a dedicated neuroimaging specialist team (CATI for “Centre pour l'Acquisition et le Traitement des Images”, http://cati-neuroimaging.com/).

- *PET images processing* - The CATI developed a pipeline allowing quantifying radiotracer uptake in the grey matter of untransformed PET images, with high throughput and a step-by-step quality check. The aim was to reduce quantification biases related to spatial normalization, co-registration and partial volume effect (PVE). MRI 3D T1-weighted images were segmented and spatially normalized into the MNI space using the VBM8 package implemented in SPM8.[13] Deformation fields, grey and white matter masks were generated and further used to define ROIs. Structural MRI images were co-registered to PET images using SPM8 with visual inspection to detect any co-registration errors. Using inverse deformation fields and matrix transformation, composite cortical ROIs and a reference region were placed in the individual native PET space. After correcting for PVE with the

RBV-sGTM method,[14] parametric PET images were created for each individual, by dividing each voxel with the mean activity extracted from the reference region.

- *PET variables* - Metabolic indexes were calculated in ROIs involving AD specific regions such as right and left precuneus, posterior cingulate cortex, associative parietal and temporal cortex, hippocampus, as well as ROIs in the frontal and occipital cortex.[15] The reference region was the pons. For amyloid PET images, standard uptake value ratios (SUVr) were calculated by averaging the mean activity of cortical ROIs: both left and right precuneus, cingulum posterior, cingulum anterior, parietal, temporal and orbitofrontal cortex. The reference region was a combination of whole cerebellum and pons regions.[16]

Statistical analysis

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

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

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

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

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

Results

Population characteristics

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

Adjustment factors and neuroimaging biomarkers

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

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

Multimorbidity and neuroimaging biomarkers

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

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

Discussion

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

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

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

different diseases clusters create different illness burden and may impact in a unique manner neurodegeneration.[24] Therefore, the type, number and severity of comorbidities may modulate the rate of atrophy and metabolism decline, being at least one important variable in a complex model of factors determining the extent of preclinical AD stage.

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

We observed that active or past smoking was associated with lower hippocampal volumes. It has been demonstrated that chronic cigarette smoking may negatively impact cognition, including memory, due to oxidative stress-induced lesions.[25] We found that a chronic excessive alcohol use was associated with lower metabolism in FDG-PET. Alcohol consumption seems to influence hippocampal neurogenesis as well as brain metabolism.[26] Intoxication states are associated with a switch in metabolism patterns, increasing acetate metabolism and reducing glucose use, as it was demonstrated in FDG-PET studies.[27] It is not clear whether these effects may be transitory or permanent in the path towards neurodegeneration.

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

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

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

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

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

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

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

Acknowledgements

Conflict of Interest:

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

Aline Mendes reports no disclosures.

Sophie Tezenas du Montcel reports no disclosures.

Marcel Levy reports no disclosures.

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

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

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

Anne Bertrand reports no disclosures.

Author contributions:

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

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

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

Hugo Bertin - PET data acquisition and analysis

Sophie Tezenas du Montcel – data analysis

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

Bruno Dubois – Interpretation and critical revision of the manuscript

Anne Bertrand – MRI data acquisition and analysis

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Table 1. Characteristics of the study population at baseline.

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)

Abbreviations: HTA = Arterial hypertension; PTSD = Post-traumatic stress disorder; BMI = Body mass index.

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

Level of education is assessed by a scale from 1 (no formal education) to 8 (at least two years post high school graduation).

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

Adjustment factors	Hippocampal volume	*P* value	FDG-PET SUV	*P* value	Amyloid-PET SUVr	*P* 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

Abbreviations: WMH = white matter hyperintensities.

Linear regression univariate analysis.

Level of education is assessed by a scale from 1 (no formal education) to 8 (at least two years post high school graduation).

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

	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
	P=0.012	*P*=0.005	*P*=0.884
	R^2=0.017	R^2=0.022	R^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
	P=0.125	*P*=0.038	*P*=0.96
	R^2=0.17	R^2=0.07	R^2=0.122
Comorbidities individually	**n=295**	**n=292**	**n=295**
	Tobbaco use	**Obesity**	**Obstructive Sleep Apnea**
	-0.081 ±0.035	-0.108 ±0.051	-0.095 ±0.043
	P=0.022	*P*=0.037	*P*=0.028
	R^2=0.018	R^2=0.041	R^2=0.016
		Excessive alcohol use	**Mood disorders**
		-0.138 ±0.049	-0.051 ±0.024
		P=0.005	*P*=0.035
		R^2=0.027	R^2=0.031
			Dyslipidemia
			0.048 ±0.022
			P=0.029
			R^2=0.047
Adjustment factors	**Age, Sex, APOE4 status**	**Age, Sex**	**Age, APOE4 status, WMH**
Comorbidities individually after adjustments	**Tobbaco use**	**Obesity**	**Obstructive Sleep Apnea**
	-0.059 ±0.035	-0.142 ±0.05	-0.084 ±0.04
	P=0.094	*P*=0.005	*P*=0.039
	R^2=0.169		
		Excessive alcohol use	**Mood disorders**
		-0.112 ±0.045	-0.053 ±0.022
		P=0.014	*P*=0.018
		R^2=0.094	
			Dyslipidemia
			0.022 ±0.02
			P=0.29
			R^2=0.148

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

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

[a] Linear regression model, 0.003 ±0.0008; $P<0.001$; $R^2= 0.12$.

[b] The association remains statistically significant after exclusion of this outlier participant from the analysis.

Abbreviations: WMH = White matter hyperintensities.