Research Article

The Association of Multimorbidity With Preclinical AD Stages and SNAP in Cognitively Unimpaired Persons

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Abstract

Background: Multimorbidity (defined as ≥ 2 chronic conditions) has been associated with increased risk of mild cognitive impairment and cross-sectionally with imaging biomarkers of neurodegeneration in cognitively unimpaired persons aged ≥ 70 years. Its association with preclinical Alzheimer's disease stages has not been studied in detail yet. The objective of the study was to assess the cross-sectional association of multimorbidity with preclinical Alzheimer's disease stages and suspected non-amyloid pathophysiology in cognitively unimpaired participants of the Mayo Clinic Study of Aging (≥ 50 years of age).

Methods: The study included 1,535 cognitively unimpaired participants with multimorbidity, ¹¹C-PiB positron emission topography and magnetic resonance imaging data available. Abnormal (elevated) ¹¹C-PiB-positron emission topography retention ratio (A+; standardized uptake value ratio >1.42) and abnormal (reduced) Alzheimer's disease signature cortical thickness (N+; <2.67 mm) were used to define biomarker combinations (A–N–, A+N–, A–N+, A+N+). Chronic medical conditions were ascertained by using the Rochester Epidemiology Project medical records linkage system and International Classification of Diseases criteria. Cross-sectional associations were examined using multinomial logistic regression models adjusting for age, sex, education, and apolipoprotein E $\epsilon 4$ allele status.

Results: Frequency of A+, N+, A+N+, and A–N+ biomarker groups increased significantly with increasing number of chronic conditions. Multimorbidity was significantly associated with A+N+ (vs A–N–; odds ratio, 1.76, 95% confidence interval 1.02, 2.90) and A–N+ (vs A–N–; odds ratio, 2.16, 95% confidence interval 1.47, 3.18). There was a dose–response relationship between increasing number of chronic conditions (eg, 0–1, 2–3, and 4+) and the odds of A+N+ and A–N+ (vs A–N–).

Conclusions: Multimorbidity was associated with biomarker combinations that included neurodegeneration with or without elevated amyloid deposition (ie, A–N+, A+N+). The associations should be validated in longitudinal studies.

Keywords: Multimorbidity, Preclinical AD, Amyloid, Neurodegeneration, SNAP

The simultaneous occurrence of multiple chronic medical conditions or multimorbidity (often defined as the coexistence of two or more chronic conditions in the same individual) is a distinctive hallmark of

aging (1) and is on the rise (2), with middle- and low-income countries progressively approaching the prevalence of multimorbidity in higher-income countries (3). Multimorbidity could also be considered (4) a

clinical marker of accelerated aging. With increasing age, there is a gradual loss of resilience and multisystem homeostatic dysregulation (4) that may increase susceptibility to multiple chronic conditions and contribute to multimorbidity. Importantly, several chronic medical conditions (eg, type 2 diabetes, hypertension, coronary artery disease [CAD], and depression), often included in multimorbidity are established risk factors for cognitive decline (mild cognitive impairment [MCI] and/or all cause and Alzheimer's disease [AD] dementia) (5,6).

Previous research in cognitively unimpaired (CU) individuals aged ≥ 70 years demonstrated that MCI or dementia risk was higher in individuals with multimorbidity, particularly in those with 4+ chronic conditions (7). In addition, faster accumulation of chronic diseases (8) over time has been associated with faster cognitive decline, and multimorbidity was also cross-sectionally associated with imaging biomarkers of neurodegeneration in those aged ≥ 70 years (9,10). Individuals with dementia have among the highest levels of co-occurring chronic conditions compared to persons with other chronic diseases (11), and multimorbidity has been associated with faster cognitive decline in patients with AD (12) and with multifaceted late-onset AD progression (ie, cognitive and functional decline and increase in neuropsychiatric symptoms) (13). Thus, researchers have suggested a dynamic relationship between multimorbidity and cognitive decline, considering multimorbidity not only at dementia diagnosis but also during the whole disease spectrum and the follow-up period (13).

Multimorbidity prevalence increases with age, but the absolute number of individuals with multimorbidity could be higher in those younger than 65 years than those 65 and older (14), underscoring its importance in clinical practice and the need for research to assess related health outcomes. As a proxy of age-related multisystem failures (8) but also as a measure of the burden of accumulated chronic conditions that are also established risk factors for MCI and/or dementia, multimorbidity may be associated with the preclinical AD stages (15–17) and suspected non-amyloid pathophysiology (SNAP) (18) even before clinically detectable cognitive decline. However, associations of multimorbidity with preclinical AD stages as defined by the National Institute on Aging and Alzheimer's Association (NIA-AA) (15) criteria have not been studied in detail. Thus, we expanded on previous studies (9,10), to include a broader age range and study the association of multimorbidity with preclinical AD stages, and SNAP in CU individuals among participants aged 50 years and older in the population-based Mayo Clinic Study of Aging (MCSA).

Methods

Study Population

Details of the design and conduct of MCSA were reported elsewhere (19). Briefly, using the Rochester Epidemiology Project resources (20), Olmsted County (Minnesota) residents, aged 70–89 years (October 1, 2004), were enumerated. They were invited to participate based on an age- and sex-stratified random sample of Olmsted County residents (19). Individuals in hospice or with a terminal illness or dementia were excluded. Study sample size was maintained by ongoing recruitment using the same protocols as in 2004. Magnetic resonance imaging (MRI) was initiated in 2005 and ^{11}C -PiB positron emission topography (PET) scans were offered to all MCSA participants beginning in 2008. In 2012, recruitment of participants aged 50–69 years was initiated. As of March 2017, we identified 1,772 MCSA participants (≥ 50 years) with available ^{11}C -PiB PET scans and multimorbidity data (at the time of first PiB PET).

Of these, 219 participants had cognitive impairment (200 had MCI and 19 had dementia) and were excluded. Of the remaining 1,553 CU participants, 99% ($N = 1,535$) also had brain MRI data. This study included 1,535 CU participants (98.1% were white; 99.3% were not-Hispanic or Latino) with available multimorbidity, ^{11}C -PiB PET, and brain MRI data.

Standard Protocol Approvals, Registrations, and Patient Consent

The MCSA study protocol was approved by the institutional review boards of the Mayo Clinic and the Olmsted Medical Center. All participants provided written informed consent before participation in the study.

Clinical Evaluation

Each participant was evaluated by a nurse or a study coordinator, a physician, and underwent neuropsychological testing by a psychiatrist. The nurse or study coordinator collected demographic information, asked questions about memory, and administered the Clinical Dementia Rating scale and the Functional Activities Questionnaire to an informant. The Short Test of Mental Status (21), review of medical history, and a neurological examination were included in the physician's evaluation. The neuropsychological testing included nine tests to assess cognitive performance in four domains: (i) memory, (ii) attention and executive function, (iii) language, and (iv) visuo-spatial skills (19,22). The nurse or coordinator, the physician, and the neuropsychologist adjudicated the final diagnosis by consensus decision after reviewing and discussing all the data for each participant (19). A diagnosis of MCI was made according to published criteria (23) and dementia was diagnosed according to *Diagnostic and Statistical Manual of Mental Disorders-IV* criteria (24). Participants were classified as CU if they performed in the normative range and did not meet criteria for MCI or dementia. Apolipoprotein E (APOE) $\epsilon 4$ allele was measured from a blood drawn at baseline assessment.

Acquisition of MRI Measures

MRI was performed at 3 Tesla and cortical surface was parcellated using FreeSurfer (v 5.3). A composite thickness measure representing an AD signature cortical thickness was computed to assess AD-related neurodegeneration based on individual cortical thickness for regions of interest from entorhinal, inferior temporal, middle temporal, and fusiform cortex from both hemispheres (25). An abnormal (reduced; N+) AD signature cortical thickness was defined as < 2.67 mm, and N– otherwise (26).

^{11}C -PiB PET Acquisition

Details are presented in previous reports (27,28). A global PiB standardized uptake value ratio was calculated from weighted median pixel values in regions of interest from both hemispheres for parietal, temporal, prefrontal, orbitofrontal, precuneus, anterior cingulate, and posterior cingulate regions and referenced to the cerebellar grey matter crus. We defined an abnormal (elevated; A+) ^{11}C -PiB-PET retention ratio as standardized uptake value ratio > 1.42 , and A– otherwise (26).

Neuroimaging Biomarker Combinations

We defined four neuroimaging biomarker combinations based on abnormal amyloid (A+/A–) and neurodegeneration (N+/N–) based on decreased AD signature cortical thickness as follows: A–N–,

A+N- (ie, NIA-AA preclinical AD stage 1), A+N+ (ie, NIA-AA preclinical AD stages 2 + 3), and A-N+ (ie, SNAP) (16,17).

Identification of Chronic Conditions

The Rochester Epidemiology Project diagnostic indices were searched electronically for each participant to identify *International Classification of Diseases, Ninth Revision and Tenth Revision (ICD-9, ICD-10)* codes, for 19 chronic conditions (29) (ie, hyperlipidemia, hypertension, depression, diabetes, arthritis, cancer, cardiac arrhythmias, asthma, CAD, substance abuse disorders [drugs and alcohol], chronic obstructive pulmonary disease, osteoporosis, chronic kidney disease, stroke, congestive heart failure, schizophrenia, hepatitis, autism spectrum disorder, and HIV infection) associated with any health care visit within 5 years before the first PiB PET scan. These conditions were chosen as they were proposed by the U.S. Department of Health and Human Services in 2010 to study multimorbidity (29). Dementia was also included in the suggested list of conditions but we excluded dementia as it was assessed by the MCSA evaluation. There were no cases of autism spectrum disorder resulting in a possible maximum of 18 chronic conditions. A chronic condition was defined as having two ICD-9 and/or ICD-10 codes for the given condition more than 30 days apart within the 5-year capture window (14).

Statistical Analysis

We examined cross-sectional associations of multimorbidity (≥ 2 conditions vs < 2) and the number of chronic conditions (eg, categorized 0–1, 2–3, and 4+ or as the total number of conditions) with the neuroimaging biomarkers' combinations (ie, A–N–, A+N–, A–N+, and A+N+). In addition, we identified the 10 most common dyads (any combinations of 2 of the 18 chronic conditions) in persons with multimorbidity and studied the association of each dyad with the

neuroimaging biomarkers' combinations. We used multinomial logistic regression models (odds ratios [ORs], 95% confidence intervals [CIs]; outcome: neuroimaging biomarkers' combinations, with reference group A–N–). The basic model was adjusted for age (at PiB PET scan), sex, and education. We adjusted additionally for APOE $\epsilon 4$ allele status in separate models. Estimates from both models did not differ appreciably; thus, we present estimates of the model adjusting for age, sex, education, and for APOE $\epsilon 4$ allele status in tables. Associations were considered significant at a two-tailed p value $< .05$. Analyses were performed using SAS statistical software, version 9.4 (SAS Institute, Cary, North Carolina) and Stata-SE statistical software, version 15.1 (StataCorp LP, College Station, Texas).

Results

Characteristics of Participants

The study sample consisted of 1,535 MCSA participants, of whom 74.1% had multimorbidity. Table 1 describes the characteristics of all participants by number of chronic conditions. Mean age (SD) was 70.4 (10.0) years, 52.7% were men, and 27.2% were APOE $\epsilon 4$ allele carriers. Nearly one third of the participants had elevated amyloid burden (A+; 29.4%) and 38.4% had neurodegeneration (N+). The frequency of total A+, total N+, A–N+, and A+N+ increased significantly with increasing number of chronic conditions.

The 10 most common chronic health conditions were hyperlipidemia (63.1%), hypertension (51.3%), arthritis (38.3%), diabetes mellitus (35.2%), cancer (22.1%), cardiac arrhythmias (19.2%), CAD (18.5%), depression (17.1%), osteoporosis (12.5%), and asthma (6.8%). The 10 most frequent dyads (pairs) of chronic conditions simultaneously present for persons with two or more chronic conditions were hypertension and hyperlipidemia, hyperlipidemia and diabetes, hypertension and diabetes, hyperlipidemia and arthritis,

Table 1. Characteristics of Participants Aged 50+ Years by Number of Chronic Conditions

Characteristics	Number of Chronic Conditions			Total (N = 1,535)	p^*
	0–1 (N = 398)	2–3 (n = 549)	≥ 4 (N = 588)		
Age, mean (SD)	64.2 (8.9)	70.1 (9.6)	75.0(8.5)	70.4 (10.0)	$< .001$
Sex, male	209 (52.5)	278 (50.6)	322 (54.8)	809 (52.7)	.378
Education (years), mean (SD)	15.3 (2.4)	15.0 (2.6)	14.4 (2.6)	18.8 (2.6)	$< .001$
APOE $\epsilon 24/\epsilon 34/\epsilon 44^\dagger$	97 (25.3)	156 (28.6)	158 (27.1)	411 (27.2)	.524
Body mass index (kg/m^2) [‡]	27.5 (4.9)	28.3 (4.7)	29.4 (5.2)	28.5 (5.0)	$< .001$
Smoker, current	26 (6.7)	23 (4.5)	24 (4.5)	73 (5.1)	$< .001$
Past	125 (32.1)	190 (36.8)	259 (48.3)	574 (39.8)	
Never	238 (61.2)	304 (58.8)	253 (47.2)	795 (55.1)	
Moderate exercise [§]					$< .001$
Once a month or never	66 (18.2)	120 (27.5)	153 (39.1)	339 (28.5)	
2–3 times/month	60 (16.5)	54 (12.4)	35 (9.0)	149 (12.5)	
$> 2-3$ times/month	237 (65.3)	262 (60.1)	203 (51.9)	702 (59.0)	
Neuroimaging A+	72 (18.1)	149 (27.1)	230 (39.1)	451 (29.4)	$< .001$
Biomarkers N+	69 (17.3)	195 (35.5)	32.6 (55.4)	590 (38.4)	$< .001$
A–N–	283 (71.1)	280 (51.0)	184 (31.3)	747 (48.7)	$< .001$
A+N–	46 (11.6)	74 (13.5)	78 (13.3)	198 (12.9)	
A–N+	43 (10.8)	120 (21.9)	174 (29.6)	337 (22.0)	
A+N+	26 (6.5)	75 (13.7)	152 (25.9)	253 (16.5)	

Note: APOE = Apolipoprotein E; N (%) unless otherwise stated; SD = Standard deviation.

*Chi-square or Kruskal–Wallis test. [†]23 missing (14 in “0–1,” 4 in “2–3,” 5 in “ ≥ 4 ” categories). [‡]8 missing (1 in “0–1,” 4 in “2–3,” 3 in “ ≥ 4 ” categories). [§]moderate exercise (ie, brisk walking, hiking, aerobics, strength training, golfing without a golf cart, swimming, tennis doubles, moderate use of exercise machines, yoga, martial arts, and weight lifting) last 12 months; 345 missing (35 in “0–1,” 113 in “2–3,” 197 in “ ≥ 4 ” categories). ^{||}A+ is defined as ¹¹C-Pittsburgh compound B standardized uptake value > 1.42 and A– if otherwise; N+ is defined as AD signature cortical thickness < 2.67 mm and N– if otherwise.

hypertension and arthritis, CAD and hyperlipidemia, hypertension and CAD, hyperlipidemia and cancer, hypertension and arrhythmias, and arthritis and diabetes. CU participants with imaging studies (PET and MRI) (vs those without imaging studies) were on average younger ($p < .001$), were more likely to be male ($p = .004$), had higher education ($p < .001$) and higher global cognitive z score ($p < .001$), and were less likely to have hypertension ($p < .001$), diabetes ($p = .015$), CAD ($p < .001$) and stroke ($p < .001$); there was no difference in frequencies of APOE $\epsilon 4$ allele carrier status, dyslipidemia, obesity, depressive symptoms, or smoking status (results not shown in tables).

Association of Multimorbidity With Neuroimaging Biomarkers' Combinations

Having multiple chronic conditions was associated with higher odds of having A+N+ and A-N+, regardless of how multimorbidity was operationalized (Table 2). Multimorbidity (defined as ≥ 2 conditions) was associated with greater odds of A+N+ (vs A-N-; OR 1.76, 95% CI 1.07, 2.90) and A-N+ (vs A-N-; OR 2.16, 95% CI 1.47, 3.18). Having more than four chronic conditions was significantly associated with A+N+ (OR 2.29, 95% CI 1.35, 3.88). There was a dose-response relationship between increasing number of chronic conditions (Table 2) and the odds of A-N+ or A+N+ (vs A-N-). The 10 most frequent dyads (regardless of other chronic conditions present) were associated with increased odds of A-N+ and A+N+ but not A+N- (vs A-N-) (Supplementary Table 1).

Discussion

Among CU participants aged ≥ 50 years, multimorbidity was associated with biomarker combinations that included neurodegeneration with or without elevated amyloid deposition (ie, A-N+, A+N+) but not A+N- (vs A-N-). These findings are consistent with previous MCSA reports in CU aged ≥ 70 years (9,10), which found an association between multimorbidity and neurodegeneration but not with amyloid positivity.

Findings are highly relevant as one in three dementia cases worldwide is attributable to diabetes, midlife hypertension, midlife obesity, depression, physical inactivity, or low educational attainment (30). Some of these chronic conditions are included in the multimorbidity

definition and represent a potentially modifiable component of dementia risk factors underscoring that preventive interventions earlier in life might be critical (14).

In this study, multimorbidity was found to be significantly associated with the A+N+ in CU individuals. We cannot exclude in present analyses that the association of multimorbidity with the A+N+ group is due to the presence of neurodegeneration and not amyloid. However, this observation is important as individuals with both elevated amyloid and neurodegeneration may have accelerated cognitive decline compared to individuals who are A-N- (16). Although older hypothetical models of AD suggest that neurodegeneration occurs downstream from amyloid accumulation (31), amyloid accumulation and neurodegeneration almost certainly occur independently (32) with amyloid accumulation subsequently accelerating neurodegeneration; once the neurodegeneration and amyloid pathways converge, then neurodegeneration is exacerbated (16). The onset of neurodegeneration in this hypothesized model could be associated with multimorbidity (9,10). This is also important considering that neurodegeneration rather than amyloid is more proximal to or directly related to cognitive symptoms (33); CU individuals with multimorbidity who are A+N+ may be good candidates for surveillance and preventive interventions when available.

Almost 22% of participants had A-N+ (ie, SNAP) on imaging, which is consistent with other studies (16). These individuals that have AD-like neurodegeneration without elevated amyloid deposition have worse cognitive outcomes than individuals without elevated levels of neurodegeneration and amyloid (18). SNAP prevalence increases with aging and a variety of non-AD processes might contribute to neurodegeneration in A-N+ individuals (eg, non-AD tauopathies, cerebrovascular disease, and synucleinopathies) (34) but the discussion is still ongoing. A previous report (35), in ≥ 70 -year-old CU MCSA individuals, did not find significant differences between A-N+ and A+N+ individuals in terms of vascular risk factors, imaging changes associated with α -synucleinopathy, or cerebrovascular imaging lesions, suggesting that neurodegeneration in CU individuals does not initially depend on β -amyloid. Although it seems that the rate of amyloid accumulation is not influenced by neurodegeneration, amyloid pathophysiology increases neurodegeneration (36); some individuals in the A-N+ group could have

Table 2. Association Between Multimorbidity and the Neuroimaging Biomarkers' Groups in Cognitively Unimpaired Participants ≥ 50 Years of Age

No. of Chronic Conditions	A+N-		A+N+		A-N+	
	No. A+N-	OR (95% CI)*	No. A+N+	OR (95% CI)	No. A-N+	OR (95% CI)
Multimorbidity [†]	195	1.10 (.74, 1.66)	252	1.76 (1.07, 2.90)	335	2.16 (1.47, 3.18)
Total number of chronic conditions	195	1.05 (.95, 1.15)	252	1.22 (1.11, 1.34)	335	1.21 (1.11, 1.30)
<i>Categorical variable</i>						
3-level multimorbidity [‡]	195	1.11 (.88, 1.40)	252	1.58 (1.23, 2.03)	335	1.60 (1.31, 1.96)
0-1 conditions [§]	44	1.00 (ref.)	26	1.00 (ref.)	42	1.00 (ref.)
2-3 conditions	74	1.05 (.68, 1.63)	75	1.32 (.77, 2.28)	119	1.79 (1.18, 2.72)
4+ conditions	77	1.21 (.76, 1.93)	151	2.29 (1.35, 3.88)	174	2.71 (1.77, 4.13)

Note: A = Amyloid; CI = Confidence interval; N = Neurodegeneration; No. = Number of individuals with the specific biomarker combinations; OR = Odds ratio.

*OR (95% CI) was retained from multinomial logistic regression; models were adjusted for age, education, sex, and APOE $\epsilon 4$ allele status; reference group, A-N-; No. A-N- = 730. [†]Defined as ≥ 2 conditions vs < 2 conditions (reference). Estimates were retained from a single multinomial logistic regression model, having the neuroimaging biomarkers' groups as the outcome variable; reference group, A-N-. [‡]3-level multimorbidity included as an ordinal variable in the multinomial model with 3 levels (0-1, 2-3, to 4+). Estimates were retained from a single multinomial logistic regression model, having the neuroimaging biomarkers' combinations as the outcome variable; reference group, A-N-. [§]3-level multimorbidity was included as a categorical variable in the multinomial model with 3 categories (0-1, 2-3, to 4+). All estimates were retained from a single multinomial logistic regression model, having the neuroimaging biomarkers' combinations as the outcome variable; reference group, A-N-.

amyloid levels that did not reach yet the cut point for positivity, but they could later present with A+N+. This is particularly important for persons with neurodegeneration in midlife who have a longer period to accumulate amyloid.

Age is one of the two most important risk factors for amyloid accumulation (together with APOE genotype) (9). The distribution of amyloid standardized uptake value ratio by age is highly skewed above age 65 years (37), and in current analyses, we deferred any age subgroup analysis until a larger sample of younger participants is accumulated. As noted earlier, the progressive loss of resilience and homeostatic dysregulation in multiple organs and systems that occurs with aging could manifest clinically as an increasing burden of multiple chronic conditions (8). In this case, multimorbidity, especially in midlife, could be a marker of accelerated aging (8), where earlier onset of age-related neurodegeneration with increasing amyloid accumulation could potentially lead to a trajectory of cognitive decline beyond that expected for their age. In addition, older adults who have accumulated multimorbidity are likely to develop neurodegeneration due to other non-amyloid etiologies, making them more vulnerable for cognitive decline at amyloid levels below the typical cut points for amyloid positivity (16).

We cannot assess causality due to the cross-sectional study design; it is plausible that multimorbidity, amyloid accumulation, and neurodegeneration are influenced by a common factor (eg, aging) and are not causally associated. However, several of the conditions in multimorbidity have been examined in previous reports for their association with AD. Although the contribution of vascular disease to amyloid accumulation remains unclear, vascular pathology is important both for the onset and the progression of dementia (38), and vascular risk factors and conditions (eg, hypertension, coronary heart disease, and diabetes) were common in the current study population and in the most frequent dyads of chronic conditions. However, additional research is needed to clarify whether there is interdependence of AD and vascular pathology (39), or whether amyloid and vascular pathologies are independent processes that affect cognitive decline in older adults (70–90 years old) (40). Research also shows that dementia and AD risk might vary with the time of onset of a vascular condition (eg, midlife) and whether treatment for that condition is in place (39), and such associations might not hold for risk factors with onset in late life (41). Individuals with early onset of cardiovascular conditions and risk factors will have ample time for synergistic or additive effects of vascular disease with AD pathology that could accelerate the trajectory toward a more advanced NIA-AA stage and cognitive decline.

This suggests the need to study individuals with accumulated multimorbidity earlier in midlife as persons potentially at high risk for future cognitive decline. It is of note, however, that persons with multimorbidity might be difficult to enroll in AD clinical trials because of their multiple medical conditions and medications. A systematic review of all ongoing randomized clinical trials, from January 1, 2014, to January 31, 2015 (data source: ClinicalTrials.gov register) (42), reported that the majority of studies for patients with chronic conditions (dementia was included) excluded patients with other concomitant chronic conditions. Specifically, among seven studies on dementia, six excluded at least one chronic condition (number of excluded conditions, median [Q1–Q3]: 10 [8–14]) and one trial targeted individuals with multiple chronic conditions (42). In addition, comorbidities and prescription medications are poorly reported in randomized controlled trials in dementia, possibly limiting generalizability of findings to the general population (43). A crisis in recruitment for Alzheimer's and dementia trials has been recognized (44)

with efforts to understand and overcome hindrances in participant enrollment. Assessing also whether current models of AD clinical trials target the most at risk groups or how our approaches may need to change to improve generalizability would be crucial.

The study has several important strengths. The ability of Rochester Epidemiology Project to capture medical record information for all Olmsted County residents who receive care in the county is a major strength of this study, reducing recall bias from self-report. State-of-the-art imaging provided reliable measures of brain pathology. Multimorbidity and biomarkers of brain amyloid and neurodegeneration were assessed in midlife for the younger participants, possibly including individuals with earlier onset of severe multimorbidity who could have been lost due to increased morbidity or mortality if assessed later in life.

The study has certain limitations. The cross-sectional design cannot assess causality. Longitudinal studies are needed to replicate current findings. There is a potential of disease misclassification due to the use of ICD-9 or ICD-10 codes, although minimized, by the use of two codes for the given condition more than 30 days apart within the 5-year capture window. We cannot assess the effects of severity of individual conditions and adequacy of management of multimorbidity on the estimated associations. The underlying mechanisms of the associations observed cannot be explored in this study and findings may not be generalizable in populations with different distribution and prevalence of chronic conditions. Participants with imaging studies (vs those without imaging studies) had a lower frequency of several chronic conditions and these differences may bias (possibly toward the null) the association between multimorbidity and neuroimaging biomarker combinations. Lastly, 98.1% of study participants were white and 99.3% were non-Hispanic or Latino; thus, assessment of these associations in more heterogeneous populations would be important.

Multimorbidity is present in three out of four persons older than 65 years and in one out of four persons younger than 65 years seeking medical care (45). As the neurodegenerative process in AD dementia precedes clinical manifestation of symptoms by several years, a major key to reducing the dementia burden could potentially be the prevention or identification and efficient management of modifiable risk factors, such as multimorbidity. However, current findings are hypotheses generating and should be assessed and validated in longitudinal studies.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

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