Multimorbidity and Risk of Mild Cognitive Impairment

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OBJECTIVES: To determine the association between multiple chronic conditions and risk of incident mild cognitive impairment (MCI) and dementia.

DESIGN: Prospective cohort study.

SETTING: Olmsted County, Minnesota.

PARTICIPANTS: Cognitively normal individuals (N = 2,176) enrolled in the Mayo Clinic Study of Aging (MCSA).

MEASUREMENTS: Participants were randomly selected from the community, evaluated by a physician, and underwent neuropsychometric testing at baseline and at 15-month intervals to assess diagnoses of MCI and dementia. Information on *International Classification of Diseases, Ninth Revision* codes for chronic conditions in the 5 years before enrollment was electronically captured using the Rochester Epidemiology Project medical records linkage system. Multimorbidity was defined as having two or more chronic conditions, and the association between multimorbidity and MCI and dementia was examined using Cox proportional hazards models.

RESULTS: Of 2,176 cognitively normal participants (mean age ± standard deviation 78.5 ± 5.2; 50.6% male), 1,884 (86.6%) had multimorbidity. The risk of MCI or dementia was higher in persons with multimorbidity (hazard ratio (HR) = 1.38, 95% confidence interval (CI) = 1.05–1.82) than in those with one or no chronic condition. The HR was of greater magnitude in persons with four or more conditions (HR = 1.61, 95% CI = 1.21–2.13) than in those with two or three conditions (HR = 1.03, 95% CI = 0.76–1.39) and for men with multimorbidity(HR = 1.53, 95% CI = 1.01–2.31) than for women with multimorbidity (HR = 1.20, 95% CI = 0.83–1.74), compared to those with one or no chronic condition.

CONCLUSION: In older adults, having multiple chronic conditions is associated with greater risk of MCI and dementia. This is consistent with the hypothesis that multiple etiologies may contribute to MCI and late-life dementia. Preventing chronic diseases may be beneficial in delaying or preventing MCI and dementia. **J Am Geriatr Soc 63:1783–1790, 2015.**

Key words: mild cognitive impairment; dementia; multimorbidity

Multimorbidity, defined as the coexistence of two or more chronic conditions in an individual,[1] is highly prevalent in older adults.[2] Estimates of prevalence increase with age and range from 55% to 98% in populations aged 60 and older.[1] Advances in the management of chronic conditions have resulted in slower disease progression and delayed mortality, resulting in an increase in the prevalence of multimorbidity.[3] The risk of disability, functional decline, premature death, poor quality of life, polypharmacy, more medical consultations, more hospitalizations, longer hospital stays, greater use of emergency care, and higher healthcare costs are all greater in individuals with multimorbidity.[1,4] Certain chronic conditions may also enhance the development of additional chronic conditions.[3]

With the growing number of individuals aged 65 and older in the United States and worldwide, the implications of the effect of multimorbidity on risk of age-related conditions such as mild cognitive impairment (MCI) and dementia are highly relevant for public health planning, allocation of resources, and development of strategies to reduce risk of these conditions. In particular, multimorbid-

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ity may contribute to greater risk of MCI, an important precursor to Alzheimer's disease and other dementias,[5–8] but the association has not been comprehensively investigated in a population-based setting. The primary objective of this study was to determine the association between multimorbidity and incident MCI and dementia in a cohort of cognitively normal individuals enrolled in the prospective population-based Mayo Clinic Study of Aging (MCSA).

METHODS

Study Cohort at Baseline

Details of the study design and methodology of the MCSA have previously been published.[9,10] Briefly, residents of Olmsted County, Minnesota, aged 70 to 89 on the prevalence (index) date (October 1, 2004) were identified using the medical records linkage system of the Rochester Epidemiology Project (REP).[11] An age- and sex-stratified random sample of eligible subjects (without dementia, not terminally ill or in hospice) was invited to participate in person or over the telephone. To maintain the study sample size, recruitment is ongoing. This study includes additional participants recruited from an enumeration of the county population on March 1, 2008, and on November 1, 2009, 2010, and 2011 using the same protocols as in 2004. The current study was restricted to participants who were evaluated in person (between 2004 and 2011), were cognitively normal at the baseline evaluation, and had at least one follow-up evaluation (N = 2,176).

Identification of MCI and Dementia

A nurse or study coordinator and a physician evaluated participants, and they also underwent neuropsychometric testing administered by a trained psychometrist. The interview by the coordinator included ascertainment of demographic information, questions about memory were administered to the participant, and the Clinical Dementia Rating scale[12] and the Functional Activities Questionnaire were administered to an informant.[13] Demographic information was also ascertained in the interview. The physician evaluation included administration of the Short Test of Mental Status,[14] a medical history review, and a complete neurological examination. Neuropsychological testing was performed using nine tests to assess performance in four cognitive domains: memory, executive function, language, and visuospatial skills.[9,10,15] Apolipoprotein E (APOE) genotype was assessed from blood drawn at baseline.

The study coordinator and physician who saw the participant and a neuropsychologist who reviewed the psychometric testing data reviewed all information collected for each participant, and a diagnosis of MCI, dementia, or normal cognition was made by consensus. Diagnoses of MCI were based on previously published criteria,[9,10,16] and diagnoses of dementia were based on *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria.[17] Participants were classified as cognitively normal if they performed in the normative range and did not meet criteria for MCI or dementia.[9,10,16]

Longitudinal Follow-Up

Follow-up was performed at 15-month intervals using the same clinical protocol for evaluation and diagnosis as at baseline. To avoid potential bias, clinical and cognitive findings from previous evaluations were not considered in making a diagnosis. Subjects who participated at baseline but declined an in-person evaluation at follow-up were invited to participate in a telephone interview that included the Telephone Interview of Cognitive Status-modified (TICS-m),[18] the Clinical Dementia Rating Scale,[12] and the Neuropsychiatric Inventory Questionnaire.[19]

Identification of Chronic Conditions

For each MCSA participant, the diagnostic indices of the REP were searched electronically to identify the *International Classification of Diseases, Ninth Revision* (ICD-9) codes associated with any healthcare visit within 5 years before enrollment (5-year capture frame). The REP captures all persons who have resided in Olmsted County, Minnesota, at any time from 1966 to the present; only 2% of residents refuse to participate at all healthcare providers. Approximately 90% of residents aged 70 and older return for a follow-up visit within 1 year after their baseline visit, ensuring excellent ascertainment of diagnosed medical conditions over the years.[20] Specific ICD-9 codes for the 19 chronic conditions (excluding dementia) that the U.S. Department of Health and Human Services proposed in 2010 for studying multimorbidity were identified for each individual.[21] A person was considered to have a specific chronic condition if they had been assigned two ICD-9 codes for the given condition separated by more than 30 days within the 5-year capture frame.[22] There were no cases of autism spectrum disorder or human immunodeficiency virus, resulting in a possible maximum of 17 chronic conditions (hyperlipidemia, hypertension, depression, diabetes mellitus, arthritis, cancer, cardiac arrhythmias, asthma, coronary artery disease, substance abuse disorders (drugs and alcohol), chronic obstructive pulmonary disease, osteoporosis, chronic kidney disease, stroke, congestive heart failure, schizophrenia, hepatitis).

Standard Protocol Approvals, Registrations, and Participant Consent

The institutional review boards of the Mayo Clinic and Olmsted Medical Center approved the study. Written informed consent was obtained from participants before participation in the study.

Statistical Analysis

Multimorbidity was defined as the presence of two or more of the 17 conditions in the 5-year capture frame. Mutually exclusive categories of comorbidity were created of participants who had no, one, two, three, or four or more of the 17 chronic conditions within the 5-year capture frame. Categories of no and one chronic condition were combined as the reference group because of the small number of subjects with no comorbidities (n = 89).

The onset of incident MCI was assigned at the midpoint between the last assessment of cognitively normal and the first-ever assessment of MCI or dementia. Subjects who progressed to dementia without an MCI diagnosis (N = 27) at an MCSA evaluation were presumed to have passed through an undetected MCI phase and included as incident cases. Subjects who refused participation, could not be contacted, or died during follow-up were censored at their last evaluation. Duration of follow-up was computed from the diagnosis of cognitively normal to first onset of MCI or dementia, censoring, or date of last follow-up.

Associations between multimorbidity and first occurrence of incident MCI or dementia were examined using Cox proportional hazards models with age as the time scale and adjustment for sex and education. Potential confounding by the APOE ε4 allele was examined, and subgroup analyses were performed according to sex. To assess interaction between age and multimorbidity, a separate Cox proportional hazards model was built with follow-up time as the time scale. Although risk of MCI or dementia was modeled, for simplicity, this outcome will be referred to as risk of MCI, hereafter. Persons with two or three chronic conditions were grouped together because risk estimates did not differ from those of persons with no or one condition. To account for incident conditions during follow-up, participants were also categorized as having multimorbidity taking into consideration incident comorbid conditions during follow-up. Finally, in persons with multimorbidity, the five most common dyads were identified (any combinations of two of the 17 chronic conditions). All analyses were considered significant at $P \leq .05$ and were performed using the SAS version 9.3 (SAS Institute, Inc., Cary, NC).

RESULTS

Of 2,176 cognitively normal participants (mean age 78.5; 50.6% male), 1,884 (86.6%) had multimorbidity (≥2 chronic conditions; Table 1). There were no differences in frequency of multimorbidity, severe multimorbidity (≥4 conditions), APOE ε4 allele, or duration of follow-up according to sex. Table 2 lists the baseline characteristics of participants according to number of chronic conditions. Mean age, frequency of obesity, and former smoking were greater with greater comorbidity. APOE ε4 genotype was not related to number of chronic conditions.

Over a median follow-up of 4 (interquartile range 2.4–6.6) years, 583 participants developed incident MCI or dementia. Multimorbidity was associated with greater risk of MCI (hazard ratio (HR) = 1.38, 95% confidence interval (CI) = 1.05–1.82) in men and women combined after adjusting for sex and education (Table 3). The HR was greater than 1.0 in men (HR = 1.53, 95% CI = 1.01–2.31) and women (HR = 1.20, 95% CI = 0.83–1.74) but was statistically significant in men only. Whether more chronic conditions increased the risk of MCI was next examined, and it was found that having four or more chronic conditions significantly increased MCI risk in both sexes combined and in men but not in women (Figure 1). APOE ε4 genotype was not a confounder of the associations.

A significant effect of the interaction between multimorbidity and sex on risk of MCI was not found in any of the analyses, although the higher estimates of risk in men than in women suggests potential effect modification according to sex. There was no statistically significant interaction between age and multimorbidity, although the risk of MCI was greater with older age or multimorbidity and of greatest magnitude in participants with the joint effect of older age and multimorbidity. Specifically, the risk of MCI was greater in participants aged 70 to 79 with multimorbidity (HR = 1.38, 95% CI = 0.94–2.02), aged 80 and older without multimorbidity (HR = 2.67, 95% CI = 1.58–4.49), and aged 80 and older with multimorbidity (HR = 3.35, 95% CI = 2.31–4.88) than in those aged 70 to 79 without multimorbidity.

In secondary analyses, multimorbidity was defined as a time dependent variable, taking into consideration chronic conditions that developed during follow-up, and the association between multimorbidity and incident MCI or dementia was explored. The risk of MCI remained high

Table 1. Characteristics of Participants at Baseline

Characteristic	All, N = 2,176	Men, n = 1,101	Women, n = 1,075
Age, mean ± SD	78.5 ± 5.2	78.2 ± 4.9	78.9 ± 5.4
Education, years, mean ± SD	14.1 ± 2.9	14.4 ± 3.2	13.7 ± 2.4
Duration of follow-up, mean ± SD	4.3 ± 2.4	4.2 ± 2.4	4.4 ± 2.4
Married, n (%)	1,431 (65.8)	936 (85.0)	495 (46.0)
Apolipoprotein E ε24/ε34/ε44, n (%)[a]	557 (25.7)	283 (25.8)	274 (25.7)
Smoking status, n (%)			
Never	1,115 (51.2)	429 (39.0)	686 (63.8)
Former	979 (45.0)	633 (57.5)	346 (32.2)
Current	82 (3.8)	39 (3.5)	43 (4.0)
Number of chronic conditions, n (%)			
0–1	292 (13.4)	147 (13.4)	145 (13.5)
2–3	700 (32.2)	348 (31.6)	352 (32.7)
≥4	1,184 (54.4)	606 (55.0)	578 (53.8)
≥2 conditions (multimorbidity), n (%)	1,884 (86.6)	954 (86.6)	930 (86.5)

[a]Information was missing for 11 participants (4 men, 7 women).

SD = standard deviation.

Table 2. Characteristics of Participants at Baseline According to Number of Chronic Conditions

Characteristic	Number of Chronic Conditions				Total, N = 2,176	*P*-Value
	0–1, n = 292	2, n = 306	3, n = 394	≥4, n = 1,184		
Age, mean ± SD	77.3 ± 4.9	77.4 ± 4.8	78.0 ± 5.0	79.3 ± 5.2	78.5 ± 5.2	<.001
Male, n (%)	147 (50.3)	154 (50.3)	194 (49.2)	606 (51.2)	1,101 (50.6)	.93
Education, years, mean ± SD	14.1 ± 3.0	14.5 ± 2.9	14.1 ± 2.9	13.9 ± 2.9	14.1 ± 2.9	.01
Smoking status, n (%)						
Never	164 (56.2)	170 (55.6)	208 (52.8)	573 (48.4)	1,115 (51.2)	.006
Former	110 (37.7)	130 (42.5)	171 (43.4)	568 (48.0)	979 (45.0)	
Current	18 (6.2)	6 (2.0)	15 (3.8)	43 (3.6)	82 (3.8)	
Body mass index ≥30.0 kg/m^2 (obese), n (%)[a]	43 (14.9)	74 (24.2)	95 (24.5)	396 (34.1)	608 (28.4)	<.001
Apolipoprotein E ε24/ε34/ε44, n (%)[b]	69 (23.7)	69 (22.7)	107 (27.3)	312 (26.5)	557 (25.7)	.40

[a]Missing information: n = 3 for 0–1 conditions, n = 7 for 3 conditions, n = 23 for ≥4 conditions.
[b]Missing information: n = 1 for 0–1 conditions, n = 2 for 2 conditions, n = 2 for 3 conditions, n = 6 for ≥4 conditions.
SD = standard deviation.

but was lower than in the primary analyses and had a wider confidence interval (HR = 1.21, 95% CI = 0.85–1.73). This may have occurred because of loss of power, because 63.4% of subjects in the reference group developed multimorbidity during follow-up.

Last, the most frequent co-occurring chronic condition pairs (dyads) in individuals with multimorbidity were identified. Overall, there were 131 dyads. The five most-common dyads were hypertension and hyperlipidemia (n = 1,096, 50.4%), hypertension and arthritis (n = 717, 32.9%), hyperlipidemia and arthritis (n = 667, 30.7%), coronary artery disease (CAD) and hyperlipidemia (n = 599, 27.5%), and hypertension and CAD (n = 555, 25.5%). In both sexes combined, the risk of MCI was significantly greater with the presence of each of the most common dyads regardless of other chronic conditions present (Table 4). In men, risk estimates for the dyads were highest for CAD and hyperlipidemia (HR = 1.75, $P = .01$) and lowest for hypertension and cancer (HR = 1.47, $P = .09$). Risk estimates for women ranged between 1.26 and 1.37, but none were statistically significant.

DISCUSSION

In this population-based prospective cohort of cognitively normal elderly persons, there was a high frequency of multimorbidity in elderly persons and a significant association between multimorbidity and risk of MCI or dementia. The risk was higher for persons with four or more chronic conditions. The risk estimates were higher in men and women, but of greater magnitude in men and statistically significant only in men. These findings emphasize the importance of preventing and effectively managing chronic diseases, provide added insights into contributors of risk for MCI and dementia, are consistent with the hypothesis that multiple etiologies may contribute to MCI and late-life dementia, and have important implications for healthcare planning and developing strategies to reduce the burden of MCI and dementia.

The majority of participants had multimorbidity (86.6%), which is in accordance with other studies[1,22] and in Olmsted County, Minnesota, in particular.[22] The initial objective was to assess multimorbidity at baseline as a predictor of MCI. The hypothesis was that long-standing chronic conditions could have subclinical and detrimental effects on brain pathology before diagnosis of MCI, although subsequent comorbidity during follow-up could affect MCI risk. The secondary analyses, taking incident multimorbidity into account, also resulted in a greater risk estimate, although the CI included 1, probably because of low power because of the smaller size of the reference group and shorter duration of follow-up after incident multimorbidity in that group. Regardless, the findings suggest that multimorbidity at older ages increases risk of cognitive decline but that longer duration of chronic disease may have a stronger effect on this decline.

The mechanisms of action were not specifically investigated, but there are several potential etiologic mechanisms that may explain the association between multimorbidity and cognitive impairment. An important potential mechanism is through cardiovascular diseases: hypertension, hyperlipidemia, and cardiac diseases, specifically CAD. A second potential mechanism is aging, an important risk factor for many chronic diseases. The HR was 3.35 in persons aged 80 and older with multimorbidity, but only 1.38 in those aged 70 to 79 with multimorbidity. Aging and age-related conditions may also co-occur with true etiological risk factors to enhance the adverse effects of those risk factors. Consistent with this, hypertension co-occurred with arthritis as one of the most-frequent dyads. The development of arthritis with aging may impair mobility in elderly persons, reducing the frequency of exercise and physical activity and possibly increasing obesity, and thereby increase the risk of cardiovascular disease and MCI.[23–26]

A third potential mechanism is the presence of two or more chronic conditions that independently or combined could synergistically promote or accelerate cognitive

Table 3. Association Between Multimorbidity and Incident Mild Cognitive Impairment or Dementia Overall and According to Sex

	Total Sample				Men				Women			
	At Risk	Events	HR (95% CI)[a]	*P*-Value	At Risk	Events	HR (95% CI)[a]	*P*-Value	At Risk	Events	HR (95% CI)[a]	*P*-Value
Conditions, n	n				n				n			
0–1	292	57	1.00 (reference)		147	25	1.00 (reference)		145	32	1.00 (reference)	
≥2	1,884	526	1.38 (1.05–1.82)	.02	954	257	1.53 (1.01–2.31)	.04	930	269	1.20 (0.83–1.74)	.33
2–3	700	149	1.03 (0.76–1.39)	.86	348	73	1.17 (0.74–1.85)	.50	352	76	0.87 (0.57–1.32)	.51
≥4	1,184	377	1.61 (1.21–2.13)	<.001	606	184	1.75 (1.15–2.66)	.009	578	193	1.43 (0.98–2.10)	.06
P-value for trend				<.001				.002				<.001

[a] Hazard ratios (HRs) and 95% confidence intervals (CIs) retained from Cox proportional hazards models adjusted for sex (where applicable) and years of education, with age as the time scale.

Figure 1. Cumulative incidence of mild cognitive impairment or dementia in participants who were cognitively normal at baseline and log rank tests comparing those with 2 or 3 and ≥4 chronic conditions with those with 0 or 1 (reference)). All participants: median age at event was 88.6 for 0 or 1 conditions, 87.8 for 2 or 3 conditions, 84.2 for ≥4 conditions. Log-rank tests (unadjusted for sex and education) were $P = .009$ for comparison of 2 or 3 with 0 or 1 conditions and $P < .001$ for comparison of ≥4 with 0 or 1 conditions. Men: median age at event was 90.1 for 0 or 1 condition, 85.9 for 2 or 3 conditions, 83.0 for ≥4 conditions. Log-rank tests were $P = .046$ for comparison of 2 or 3 with. 0 or 1 conditions and $P < .001$ for comparison of ≥4 with 0 or 1 conditions. Women: median age at event was 86.9 for 0 or 1 conditions, 89.1 for 2 or 3 conditions, 85.2 for ≥4 conditions. Log-rank tests were $P = .06$ for comparison of 2 or 3 with 0 or 1 condition and $P < .001$ for comparison of ≥4 with 0 or 1 condition.

decline. For example, heart disease is a risk factor for overt and subclinical cerebrovascular disease, and presence of both conditions may have worse effects on risk of cognitive impairment than just one.[27–29] A recent study suggested that cardiovascular disease is an important risk factor for arthritis.[30] Thus, the combined presence of cardiac disease and arthritis may act synergistically to increase or accelerate the risk of MCI. Alternatively, a condition may not necessarily be an established risk factor for MCI but, in combination with a risk factor, may increase the risk of MCI. For example, one study reported

Table 4. Association Between Chronic Disease Dyads and Incident Mild Cognitive Impairment or Dementia, Overall and According to Sex

Dyads[a]	At Risk	Events	Hazard Ratio (95% Confidence Interval)[b]	*P*-Value
	n			
Total sample				
Hypertension and hyperlipidemia	1,388	385	1.50 (1.13–1.99)	.005
Hypertension and arthritis	1,009	284	1.54 (1.15–1.07)	.004
Hyperlipidemia and arthritis	959	261	1.58 (1.18–2.13)	.002
CAD and hyperlipidemia	891	246	1.56 (1.15–2.10)	.004
Hypertension and CAD	847	229	1.51 (1.11–2.05)	.009
Men				
Hypertension and hyperlipidemia	714	184	1.60 (1.04–2.44)	.03
Hypertension and cancer	468	111	1.47 (0.94–2.31)	.09
Hyperlipidemia and cancer	465	113	1.61 (1.20–2.23)	.04
CAD and hyperlipidemia	541	151	1.75 (1.13–2.70)	.01
Hypertension and CAD	506	137	1.67 (1.70–2.59)	.02
Women				
Hypertension and hyperlipidemia	674	201	1.37 (0.93–2.01)	.11
Hypertension and arthritis	563	162	1.28 (0.86–1.91)	.22
Hyperlipidemia and arthritis	511	141	1.33 (0.89–2.01)	.17
Hypertension and osteoporosis	408	122	1.28 (0.84–1.95)	.26
Hypertension and diabetes mellitus	401	107	1.26 (0.83–1.92)	.28

[a]Most-common pairs of chronic conditions simultaneously present for persons with two or more chronic conditions.
[b]From Cox proportional hazards models adjusted for sex (where applicable) and years of education, using age as the time scale. Reference group was people who had 0 or 1 chronic condition.
CAD = coronary artery disease.

that several conditions that are not known risk factors for MCI or dementia contributed to a high frailty index, which in turn was associated with greater risk of dementia.[31] This suggests that a high burden of illness may increase the risk of cognitive impairment and that improving overall health might have a beneficial effect on the burden of late-life cognitive impairment or dementia.[31]

Finally, use of multiple prescription medications in persons with multimorbidity may contribute to risk of MCI and dementia. Clinical guidelines typically focus on a single disease, and adherence to these guidelines could result in adverse interactions between drugs and diseases.[32] Failure to manage specific chronic conditions optimally (e.g., cardiovascular disease or diabetes mellitus) or to take into account the different medications used in treatment of these conditions in an individual could contribute to risk of cognitive impairment.[33,34]

The current findings are consistent with studies showing associations between several chronic diseases and cognitive decline and impairment. Specifically, previous research in the MCSA shows that chronic diseases such as cardiac disease,[35] type 2 diabetes mellitus,[36] cerebrovascular disease,[37] depression,[38] and chronic obstructive pulmonary disease[39] are risk factors for MCI. Several of these chronic conditions are established risk factors for dementia (e.g., hypertension, cerebrovascular disease, dyslipidemia, type 2 diabetes mellitus)[40,41] and for MCI[42] and were included in multimorbidity in the present study.

Other studies have reported similar associations between chronic conditions and cognitive impairment or dementia. Comorbidity was associated with faster cognitive decline in individuals with Alzheimer's disease[43] and was cross-sectionally associated with greater Alzheimer's disease severity.[44] Persons with cognitive impairment, no dementia or with dementia were reported to have more-serious comorbidities than cognitively normal individuals, and the severity of comorbidity was associated with worse daily functioning and cognition.[45] In another study, multimorbidity was significantly associated with faster decline in daily functioning in individuals with dementia than in those without.[46] Effects of multimorbidity on functioning in individuals with dementia could result in greater disability than expected, possibly due to disturbances in normal compensatory physiological mechanisms.[47]

The sex difference indicating a stronger association of multimorbidity with incident MCI and dementia in men may be due to effect modification because the frequency of multimorbidity was similar in men and women. Men may have had more-severe comorbidity at enrollment or longer duration of comorbidity, or the effects of comorbidity on brain pathology leading to MCI risk may differ in men and women. Some studies suggest that there are sex differences in risk factors and health outcomes such as cardiovascular disease,[48,49] with men being younger at the time of myocardial infarction or stroke than women.

The study has certain potential limitations. One limitation is the potential misclassification due to use of ICD-9 codes to define chronic conditions. To obviate this, two ICD-9 codes were required for a given condition separated by more than 30 days within the 5-year capture frame. There was limited power for subgroup analyses according to sex, but longer follow-up and more MCI and dementia events should increase the power and precision of the estimates. Finally, study participants were primarily Caucasian, so caution should be used in generalizing findings to ethnicities not represented, although the findings suggest a hypothesis for investigation in other ethnicities.

The current study has several strengths. The MCSA is a large, prospective, population-based study. Participants undergo a comprehensive evaluation by three independent evaluators to assess MCI or dementia by a consensus decision. The evaluators at follow-up are blinded to previous clinical findings, which reduces misclassification and diagnostic bias and enhances the internal validity of the study findings. The ability of the REP to capture medical information for all Olmsted County residents who receive care in the county, with more than 90% of persons aged 70 and older returning in a 3-year period, is an important strength that results in excellent ascertainment of multimorbidity over time.[20] The use of the REP medical records linkage system to identify relevant ICD-9 codes of all chronic conditions within 5 years of enrollment reduced the temporal ambiguity in diagnoses and allowed the association between multimorbidity and MCI and dementia to be examined prospectively. In addition, data on chronic conditions were prospectively identified from ongoing medical care and therefore could have eliminated recall bias.

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Author Contributions: Roberts had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Roberts, St. Sauver, Knopman, Petersen, Vassilaki: study concept and design. Petersen, Vassilaki, Knopman, Roberts: data acquisition. Vassilaki, Aakre, Cha, Kremers, Roberts: data analysis and interpretation. Vassilaki, Roberts: drafting the manuscript. Vassilaki, Cha, St. Sauver, Mielke, Geda, Machulda, Petersen, Roberts: critical revision of manuscript for important intellectual content. Cha, Roberts: statistical analysis. Roberts, Petersen: obtaining funding. All authors approved the final version of the manuscript before submission and will approve the final version to be published.

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