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RESEARCH ARTICLE

Trajectory of multimorbidity before dementia: A 24-year follow-up study

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Abstract

INTRODUCTION: Although the multimorbidity–dementia association has been widely addressed, little is known on the long-term trajectory of multimorbidity (TOM) in preclinical dementia.

METHODS: Based on the Health and Retirement Study, burden of multimorbidity was quantified with the total number of eight long-term conditions (LTC). Patterns of TOM before dementia diagnosis were investigated with mixed-effects models.

RESULTS: In 1752 dementia cases and 5256 matched controls, cases showed higher and faster increasing predicted number of LTC than controls, with a significant case–control difference from 20 years prior to dementia diagnosis. Larger increases in number of LTC during preclinical phase of dementia were found in White participants, females, those whose age at dementia onset was younger, and those who were less educated.

DISCUSSION: Our findings emphasize the faster accumulation of multimorbidity in prodromal dementia than in natural aging, as well as effect modifications by age and sex.

KEYWORDS
dementia, epidemiology, multimorbidity, trajectory

Highlights

1. TOM increased faster in prodromal dementia than in natural ageing.
2. Patterns of TOM by dementia status diverged at 20 years before dementia diagnosis.
3. Patterns of TOM were modified by age and sex.

1 | INTRODUCTION

Global forecasting data indicate that the number of people living with dementia will increase from ≈ 57 million in 2019 to 152 million in 2050.[1] The number of deaths due to dementia ranked seventh globally in 2019, and increased largely during the past three decades.[2] Due to the absence of effective medical treatments, identification of early signs of dementia is critical for dementia prevention.[3] The

pathophysiological hallmarks, such as amyloid beta and tau deposition, begin more than two decades prior to the onset of Alzheimer's disease (AD).[4] Interventions at the earliest possible stage have been proposed to prevent or delay dementia.[3]

Multimorbidity, defined as the coexistence of at least two long-term conditions (LTC) in the same individual, is strongly associated with age, with a prevalence of 65% in adults aged 65 to 84 years and 81% in those aged ≥ 85 years.[5] There is growing consensus that heavier burden of multimorbidity is associated with increased risks of memory decline,[6] cognitive decline,[7,8] and incident dementia.[9,10] A single-time-point measurement of multimorbidity at baseline was used in the previous studies.[6–8,10] It has been reported that a steeper increase in multimorbidity was associated with higher dementia incidence in a cohort study;[9] however, differences in the preceding-dementia-onset time windows of multimorbidity burden between demented and non-demented individuals were not examined.[9] Some previous studies have focused on trajectory of a single chronic condition including depression,[11] stroke,[12] blood pressure, cholesterol, and glucose[13] before dementia occurrence. The temporal pattern of multimorbidity during the preclinical phase of dementia is largely unknown. Understanding the multimorbidity trajectory before dementia onset is useful to identify people at high risk of dementia and to find the optimal time window for dementia prevention.

Based on longitudinal data of the Health and Retirement Study (HRS), we aimed to explore the trajectory of multimorbidity (TOM), which was repeatedly measured over a period of 24 years preceding the dementia diagnosis. Because the prevalence and incidence of dementia vary by age, sex, race, education, and apolipoprotein E (*APOE*) ε4,[14–16] we also aimed to examine whether TOM before dementia is modified by these factors.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed literature on the trajectory of multimorbidity and dementia. Previous studies focused on associations between multimorbidity and risks of incident dementia. However, there were no studies that examined the temporal pattern of multimorbidity during the preclinical phase of dementia, as well as limited evidence on the effect modification by race, sex, age at dementia diagnosis, education, and apolipoprotein E ε4.
2. **Interpretation**: Our results indicated that multimorbidity burden increased faster in prodromal dementia than in natural aging, especially in females and those whose age at dementia onset was <n 75 years.
3. **Future directions**: Future interventional studies can help to further our understanding of the optimal time windows for multimorbidity intervention in dementia prevention. Prospective studies with more chronic conditions are warranted to confirm our findings.

2 | METHODS

2.1 | Study population

This study is embedded in the HRS, an ongoing, nationally representative, longitudinal cohort of US population-based adults aged ≥ 50 years.[17] The HRS has been conducted biennially since 1992 to collect a wide range of information on employment, wealth, family composition, lifestyle, and health status. The response rate in the follow-up of HRS was ≈ 85%.[17] The modified Telephone Interview for Cognitive Status (TICS-m), used for the classification of cognitive function in HRS,[18] has been measured since wave 3. As a result, 24-year data from wave 3 (1996) to wave 15 (2020) were available for the longitudinal data analysis. The HRS was ethically approved by the University of Michigan Institutional Review Board. All participants provided informed consent for participation in the study.

2.2 | Assessment on multimorbidity

History of doctor-diagnosed chronic diseases was surveyed at each study wave. Participants were asked "Has a doctor ever told you that you have … ." Seven common LTC were assessed, including hypertension, diabetes, cancer (except skin cancer), lung disease, heart problems (heart attack, coronary heart disease, angina, congestive heart failure, or other heart problems), stroke, and arthritis. Multimorbidity was defined as having ≥ 2 LTC.

2.3 | Dementia diagnosis

Dementia status was determined following methods used in previous studies.[18,19] Cognitive function was assessed with the TICS-m, which included three tests of serial sevens subtraction, immediate and delayed recall items, and counting backward. Total scores of TICS-m were calculated by summing the scores of each cognitive test (0 to 27 points), with higher scores indicating better cognitive performance. TICS-m is validated for dementia screening and has been widely applied in previous studies using HRS data.[18,19] According to the criteria of Langa–Weir Classification of cognitive function, dementia was defined as having TICS-m scores < 6.[18,19]

In addition, for proxy respondents, composite cognitive scores were calculated with proxy assessment of memory levels (excellent, very good, good, fair, poor; 0 to 4 points), limitations in five instrumental activities of daily living (taking medication, managing money, cooking, using phone, and shopping; 0 to 5 points), and the interviewer assessment of whether the respondents had cognitive impairment (no, maybe, yes; 0 to 2 points). Total scores of proxy assessment were calculated, ranging from 0 to 11, with higher scores meaning poorer cognitive function. Participants who had proxy assessment scores ≥ 6 were classified as demented.[19]

2.4 | Covariates

The demographic information on age (years), sex (male, female), race/ethnicity (White/Caucasian, Black/African American, or other), and years of education were obtained via structured questionnaires. *APOE* ε4 carriers were those who had either one or two ε4 alleles.

2.5 | Matched nested case–control sample

Among 13,395 participants surveyed during HRS waves 3 through 15, we excluded individuals who were < 50 years at cohort entry ($n = 1519$), had prevalent dementia at wave 3 ($n = 1162$), had assessments on dementia status for fewer than two times ($n = 698$), or had missing data on covariates ($n = 11$; Figure S1 in supporting information). A total of 10,005 participants remained for matching, of whom 2133 with incident dementia were identified.

Dementia cases had to develop incident dementia during follow-up visits, and to be dementia free at the previous visit of dementia diagnosis to ensure it was the onset of dementia. Controls met the following criteria: they were dementia free across waves; they were dementia free at the visit of diagnosis of the matched dementia case and at one or more visits before the matching visit, to ensure they were dementia free until the matching visit; and they matched to a dementia case by race, age (± 3 years), sex, years of education, and study wave. Time (in years) before dementia at each visit was calculated by subtracting visit year before matching visit from the year at matching visit for each matching pair. Time 0 corresponds to the matching visit for cases and controls. Each dementia case was matched to three controls at the visit of dementia diagnosis. Random sampling with replacement between visits was used to select controls according to a previous study.[13] The R package "MatchIt" version 4.4.0 was used to match controls to cases with the nearest neighbor matching with replacement. Finally, 1752 dementia cases were successfully matched to three controls each, resulting in a total sample of 7008 individuals.

2.6 | Statistical analysis

The method of Spearman correlation was applied to estimate correlations between the difference (dementia – non-demented) in prevalence of multimorbidity category (≥ 1, ≥ 2, ≥ 3, ≥ 4, and ≥ 5 chronic conditions) and time to dementia diagnosis. The TOM before dementia was estimated using mixed-effects regression models, adjusting for age, sex, race, and years of education. Random intercept and slope on time were used to correct the intra-individual correlation caused by repeated measurements. In the regression model, number of LTC was used as the dependent variable and items of dementia status, time, and "dementia × time" interaction were used as predictors. Natural cubic splines of time were used to fit the trajectory curves. To examine effects modified by race, a three-way interaction term of "dementia × time × race" was included in the regression model. The significance of interaction terms was examined with the Wald test. Similar methods were applied to test modification of other factors including age at dementia diagnosis (mean = 74.08 years, cut-off at 75 years), sex, years of education (mean = 11.19 years, cut-off at 10 years), and *APOE* ε4 allele status ($n = 5157$).

The mean predicted number of LTC between cases and controls were compared at different time points, and *P* values were adjusted with false discovery rate (FDR) due to multiple comparisons. Sensitivity analyses were performed when using a 1:1 matching ratio to obtain a nested case–control sample (1892 cases and 1892 matched controls), and when additionally adjusting for other covariates including marital status, smoking, drinking, body mass index (BMI), physical activity, and disability. Data analysis was performed with R version 4.2.1.

3 | RESULTS

3.1 | Characteristics of participants

Characteristics of participants at the visit of dementia diagnosis are shown in Table 1. The nested case–control sample was composed of 1752 dementia cases and 5256 matched controls. Participants had an average of 7.22 (standard deviation [SD] = 3.32) measurements on multimorbidity over a mean follow-up time of 12.80 years (SD = 6.67, range = 2 to 24 years). The mean age at dementia diagnosis was 74.26 years (SD = 7.65) among dementia cases. Males and White individuals accounted for 52.00% and 72.72%, respectively. Participants had an average of 11.19 years of education. Differences in age at dementia diagnosis, sex, race, and years of education between cases and controls were not statistically significant. Compared to controls, dementia cases had a higher number of LTC, had lower levels of alcohol drinking, BMI, physical activity, and TICS-m scores, and were more likely to be *APOE* ε4 carriers, to be smokers, to be separated/divorced/widowed, and to be physically disabled (all $P < 0.05$). Dementia cases also had significantly higher proportions of hypertension, diabetes, lung disease, heart problems, stroke, and arthritis.

3.2 | Prevalence of multimorbidity category before dementia

We found that observed prevalence of multimorbidity increased with retrospective time to dementia diagnosis (Figure 1). Compared to controls, dementia cases had higher prevalence of multimorbidity throughout the whole study period. Prevalence of participants who had ≥ 3, ≥ 4, and ≥ 5 chronic conditions elevated faster in dementia cases than in controls, especially when approaching the onset of dementia. Time to dementia diagnosis was significantly positively correlated with the dementia-status-related differences in prevalence of ≥ 3 LTC ($r = 0.85$, $P < 0.001$), ≥ 4 LTC ($r = 0.99$, $P < 0.001$), and ≥ 5 LTC ($r = 0.98$, $P < 0.001$; Figure S2 in supporting information).

3.3 | Trajectory of LTC number before dementia

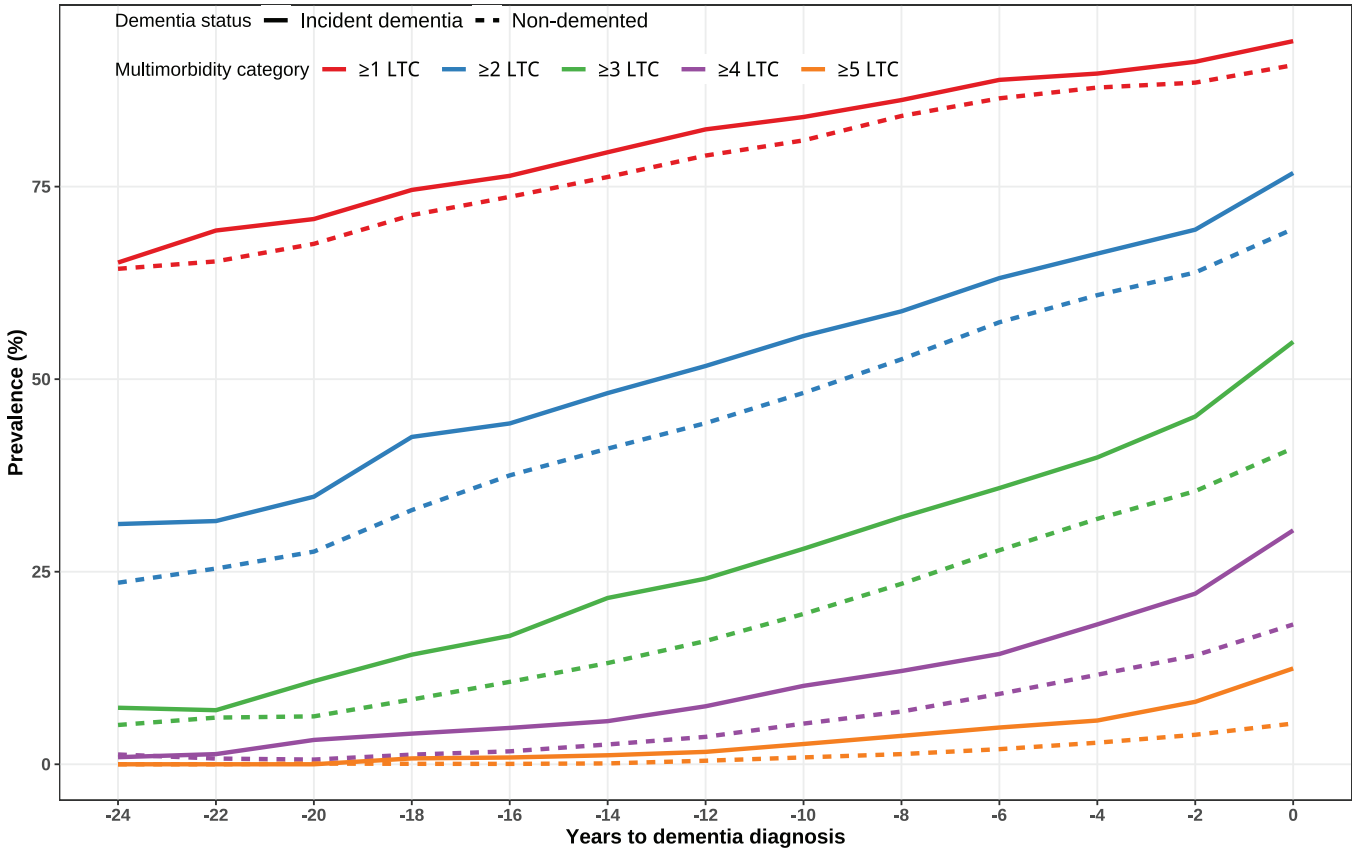
The predicted mean number of LTC significantly increased over time for dementia cases and controls (Figure 2; $P < 0.001$ for time).

TABLE 1 Characteristics of participants at dementia diagnosis.

Characteristics	Total ($n = 7008$)	Non-demented ($n = 5256$)	Incident dementia ($n = 1752$)	*P* value
Number of LTC, mean (SD)	2.37 (1.40)	2.26 (1.35)	2.72 (1.49)	< 0.001
Age at dementia diagnosis (years), mean (SD)	74.08 (7.48)	74.01 (7.43)	74.26 (7.65)	0.228
Category of age at dementia, *n* (%)				0.526
< 75 years	3426 (48.89%)	2581 (49.11%)	845 (48.23%)	
≥ 75 years	3582 (51.11%)	2675 (50.89%)	907 (51.77%)	
Sex, *n* (%)				1.000
Male	3644 (52.00%)	2733 (52.00%)	911 (52.00%)	
Female	3364 (48.00%)	2523 (48.00%)	841 (48.00%)	
Race/ethnicity, *n* (%)				1.000
White/Caucasian	5096 (72.72%)	3822 (72.72%)	1274 (72.72%)	
Black/African American	1704 (24.32%)	1278 (24.32%)	426 (24.32%)	
Other	208 (2.97%)	156 (2.97%)	52 (2.97%)	
Years of education, mean (SD)	11.19 (3.17)	11.19 (3.17)	11.19 (3.17)	1.000
Category of years of education, *n* (%)				1.000
< 10 years	1808 (25.80%)	1356 (25.80%)	452 (25.80%)	
≥ 10 years	5200 (74.20%)	3900 (74.20%)	1300 (74.20%)	
APOE ε4[a]				< 0.001
Non-carrier	3695 (71.65%)	3008 (75.09%)	687 (59.69%)	
Carrier	1462 (28.35%)	998 (24.91%)	464 (40.31%)	
Marital status, *n* (%)				< 0.001
Married/partnered	4104 (58.56%)	3152 (59.97%)	952 (54.34%)	
Separated/divorced/widowed	2684 (38.30%)	1942 (36.95%)	742 (42.35%)	
Never married	220 (3.14%)	162 (3.08%)	58 (3.31%)	
Smoking status, *n* (%)				0.012
Never	2754 (39.87%)	2116 (40.84%)	638 (36.94%)	
Past	3352 (48.52%)	2482 (47.91%)	870 (50.38%)	
Current	802 (11.61%)	583 (11.25%)	219 (12.68%)	
Drinking (drinks per week), mean (SD)	1.97 (5.88)	2.20 (6.19)	1.28 (4.75)	< 0.001
BMI (kg/m^2), mean (SD)	27.65 (5.60)	27.96 (5.37)	26.74 (6.15)	< 0.001
Physical activity scores, mean (SD)	5.86 (6.15)	6.55 (6.24)	3.73 (5.32)	< 0.001
Disability, *n* (%)				< 0.001
No	5287 (75.44%)	4327 (82.32%)	960 (54.79%)	
Yes	1721 (24.56%)	929 (17.68%)	792 (45.21%)	
TICS-m scores, mean (SD)	12.85 (4.88)	14.58 (3.71)	7.63 (4.22)	< 0.001
LTC components, *n* (%)				
Hypertension	4657 (66.45%)	3433 (65.32%)	1224 (69.86%)	< 0.001
Diabetes	1892 (27.00%)	1319 (25.10%)	573 (32.71%)	< 0.001
Cancer	1398 (19.95%)	1029 (19.58%)	369 (21.06%)	0.178
Lung disease	911 (13.00%)	641 (12.20%)	270 (15.41%)	< 0.001
Heart problems	2196 (31.34%)	1518 (28.88%)	678 (38.70%)	< 0.001
Stroke	898 (12.81%)	467 (8.89%)	431 (24.60%)	< 0.001
Arthritis	4676 (66.72%)	3463 (65.89%)	1213 (69.24%)	0.010

Abbreviations: %, proportion; *APOE*, apolipoprotein E; BMI, body mass index; LTC, long-term conditions; n, frequency; SD, standard deviation; TICS-m, modified Telephone Interview for Cognitive Status.

[a]There were 1851 participants who had missing data on *APOE* ε4.



Number of participants by dementia status, multimorbidity category, and years to dementia diagnosis

Dementia status	Multimorbidity category	-24	-22	-20	-18	-16	-14	-12	-10	-8	-6	-4	-2	0
Non-demented	All participants	314	677	1141	1606	2085	2611	3037	3484	3859	4189	4605	5096	5256
Non-demented	≥1 LTC	202	442	771	1145	1536	1991	2400	2822	3248	3622	4046	4510	4771
Non-demented	≥2 LTC	74	172	315	530	782	1070	1345	1680	2029	2404	2805	3254	3653
Non-demented	≥3 LTC	16	41	71	135	223	343	486	680	904	1164	1467	1807	2157
Non-demented	≥4 LTC	4	5	7	20	35	67	108	184	264	383	535	720	954
Non-demented	≥5 LTC	0	0	1	1	1	3	14	31	51	82	129	195	278
Incident dementia	All participants	109	228	380	527	678	857	996	1140	1272	1383	1531	1752	1752
Incident dementia	≥1 LTC	71	158	269	393	518	681	821	958	1097	1229	1373	1598	1645
Incident dementia	≥2 LTC	34	72	132	224	300	413	515	634	748	873	1015	1216	1345
Incident dementia	≥3 LTC	8	16	41	75	113	185	240	319	408	496	610	791	961
Incident dementia	≥4 LTC	1	3	12	21	32	48	75	116	154	198	278	388	532
Incident dementia	≥5 LTC	0	0	0	4	6	10	16	30	47	66	87	142	218

FIGURE 1 Observed prevalence of multimorbidity category before dementia diagnosis. Participants were categorized into different groups according to the number of LTC at each study wave. Observed prevalence of multimorbidity category (*y* axis) was plotted against years to dementia diagnosis (*x* axis). Prevalence of dementia cases and controls are shown in solid and dashed lines, respectively. "All participants" in the table at bottom means the number of participants who had LTC measurements. LTC, long-term conditions

Compared to controls, cases had a consistently higher predicted number of LTC during the whole study period ($P < 0.001$ for "dementia × time" interaction), with significant differences in a long window spanning from −20 years to dementia diagnosis onward (FDR-adjusted $P < 0.05$; Figure S3 in supporting information). The predicted mean number (95% confidence interval [CI]) of LTC was, respectively, 2.22 (2.17 to 2.27) and 2.36 (2.32 to 2.41) at −24 and 0 years to dementia onset for controls, and 2.32 (2.25 to 2.38) and 2.64 (2.58 to 2.69) at −24 and 0 years to dementia onset for dementia cases. We found nearly parallel TOM by dementia status from 24 to 20 years before dementia diagnosis and faster increases in LTC number from −20 years to dementia diagnosis for dementia cases.

White participants with incident dementia had heavier burden of multimorbidity compared to non-demented individuals, reflected

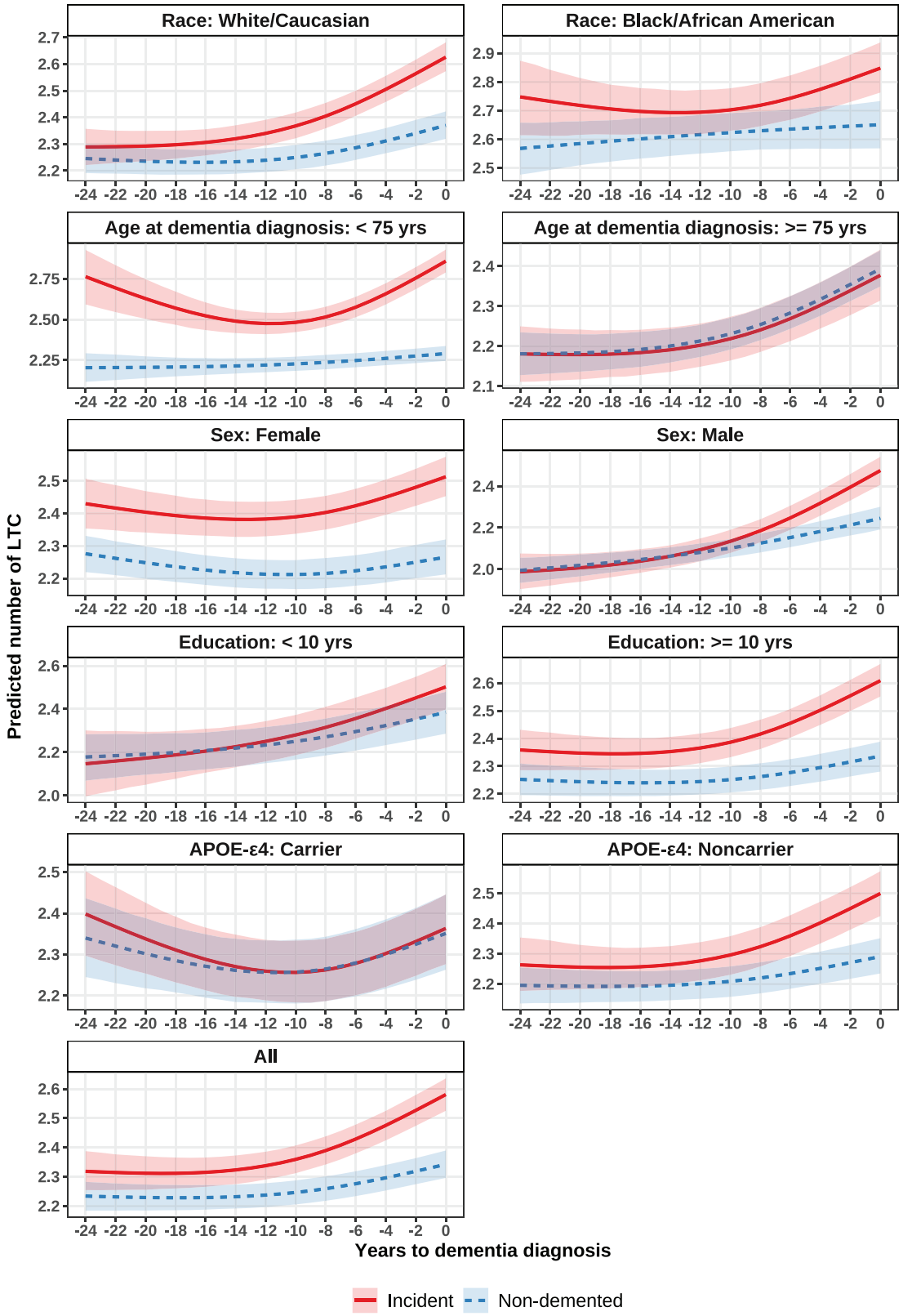


FIGURE 2 Predicted mean trajectories of number of LTC before dementia diagnosis. Predicted number of LTC was estimated using mixed-effects models among dementia cases ($n = 1752$) and matched controls ($n = 5256$), adjusting for age at dementia, sex, race, and years of education. Trajectories were plotted for participants with the following profile: female, 74.08 years old, White/Caucasian, and 11.19 years of education. Trajectories for dementia cases and controls are presented in red solid and blue dashed lines, respectively. *APOE*, apolipoprotein E; LTC, long-term conditions

by an accelerated increase in LTC number around 16 years before diagnosis, which became significant from 13 years before diagnosis onward (FDR-adjusted $P < 0.001$). In the Black individuals, LTC number was not significantly different between cases and controls over time (FDR-adjusted $P > 0.05$).

Three-way interaction between age at dementia diagnosis, time, and dementia status was statistically significant, suggesting the modification of age at diagnosis ($P_{\text{interaction}}$ for continuous age < 0.001, $P_{\text{interaction}}$ for categorical age [< 75, ≥ 75 years] < 0.001). Among participants whose age at dementia diagnosis < 75 years, dementia cases had significantly higher number of LTC throughout the whole study period (FDR-adjusted $P < 0.001$). However, no significant difference in LTC number was found between cases and controls among those with age at dementia diagnosis at ≥ 75 years.

Sex-specific TOM was found ($P < 0.001$ for "dementia × time × sex" item). Female cases started with significantly higher number of LTC and had a faster increase than female controls (FDR-adjusted $P < 0.05$ over follow-up). We found that males showed similar levels of LTC between demented and non-demented participants from −24 to about −12 years to diagnosis, and then demented cases had an accelerated increase, leading to a significant difference from 5 years before diagnosis onward (FDR-adjusted $P < 0.05$).

We found non-significant modification of years of education on TOM ($P_{\text{interaction}}$ for continuous duration of education $= 0.362$, $P_{\text{interaction}}$ for categorical duration of education [< 10, ≥ 10 years] $= 0.554$). The predicted number of LTC was not significantly different by dementia status over time among participants with low education (< 10 years; FDR-adjusted $P > 0.05$). Our results revealed that dementia cases educated for at least 10 years had a higher LTC number than controls over time, with a significant difference since −19 years to diagnosis (FDR-adjusted $P < 0.05$).

Patterns of TOM were not significantly modified by *APOE* ε4 allele status ($P_{\text{interaction}} = 0.222$). From −3 years to dementia diagnosis onward, *APOE* ε4 non-carriers with dementia had a significantly higher number of LTC compared to dementia-free non-carriers (FDR-adjusted $P < 0.05$). However, trajectory patterns between cases and controls were not significantly different over time among *APOE* ε4 carriers.

Compared to the primary results, similar patterns of TOM were found when each dementia case was matched by one control (Figure S4 in supporting information), and when additionally adjusting for marital status, smoking, drinking, BMI, physical activity, and disability (Figure S5 in supporting information).

4 | DISCUSSION

Based on the prospective cohort spanning 24 years in middle-aged and older adults, results indicated that multimorbidity burden generally increased faster in participants with incident dementia compared to matched non-demented controls, with a significant difference at 20 years preceding dementia diagnosis. Moreover, patterns of TOM during the preclinical phase of dementia were modified by age and sex.

Among all participants, we found that the preclinical trajectory of increase in multimorbidity started at −20 years to dementia diagnosis. Temporal patterns of a single chronic condition during the preclinical phase of dementia have been examined previously.[11–13] Results from a case–control study nested in the Three-City Study showed lower levels of systolic blood pressure, lower levels of diastolic blood pressure, and higher glucose levels in dementia cases than in controls at about 3, 4, and > 14 years prior to diagnosis, respectively.[13] Researchers also found that risks of dementia started to increase 5 years before stroke occurrence in women.[12] Our findings highlighted that a faster accumulation of multimorbidity seems to be associated with dementia onset. Chen et al. classified participants from the HRS into four patterns of TOM and found that individuals with steeper increase in multimorbidity had increased risks of dementia.[9] However, time windows during which multimorbidity burden diverged between dementia cases and controls have not been investigated previously.

In the stratification analysis by race, the most apparent divergence in TOM by dementia status was found among White participants. Data from National Alzheimer's Coordinating Center suggested that compared to demented White people, demented Black individuals had more dementia risk factors and more severe cognitive impairment and symptoms,[20] which was in accordance with our findings that Black participants generally had higher numbers of LTC than White individuals over time (Figure 2). Consequently, weak case–control differences in TOM among Black participants might be induced by the heavy burden of multimorbidity in Black controls. We found that pattens of TOM were not significantly modified by race, which should be explained with caution due to the limited sample size in Black individuals ($n = 1704$) and other races ($n = 208$) in this study.

A significant difference in the number of LTC was found in participants who developed incident dementia at the age of < 75 years. Data from a previous study indicated that associations of stroke and low systolic blood pressure with dementia risks were statistically significant in cases with onset age of dementia ≤ 87 years but not in those with onset age of dementia > 87 years.[21] Another study found that multimorbidity-associated risks of dementia were stronger in participants whose multimorbidity occurred in mid-life than those in late life.[22] Consequently, age-specific disparities in TOM could be explained by stronger associations between multimorbidity and dementia risks in the early stage of dementia process than that in late stage.

Our results showed that female cases had a consistently higher number of LTC than controls over the whole study period starting from −24 years to dementia diagnosis, and that significant case–control difference started at 5 years before diagnosis for males. The prevalence of dementia is about 1.9 times greater in women than in men.[23] Compared to men, heavier burden of dementia in women is presumed to be caused by multiple scenarios including stronger effects of *APOE* ε4 on cognitive declines and AD pathology, more common risk factors (e.g., lower educational attainment, less physical exercise, more depression), and reproductive factors (e.g., hypertensive disorders, menopause, and hormone replacement therapy).[24] Although sex disparities in multimorbidity and dementia have been widely addressed, the biological mechanisms of sex disparities in TOM before dementia have not been

elucidated. Our results highlighted that multimorbidity intervention should be performed earlier in females than in males for dementia prevention.

More apparent differences in trajectory patterns by dementia status were found in higher-educated participants than in lower-educated ones, but without significant modification effects of education. It has also been reported that associations between middle-age cardiovascular burden and old-age cognition[25] were modified by educational attainment. In addition, less education is regarded as a risk factor for dementia[3] and multimorbidity.[26] Differences in TOM between cases and controls might be offset and masked by the detrimental effects of less education in participants who had lower levels of education.

We found that dementia cases had significantly higher number of LTC than controls at 3 years before dementia diagnosis in *APOE* ε4 non-carriers but not in carriers, with a non-significant interaction item of "dementia × time × *APOE* ε4." Similarly, it has been reported that associations between ideal cardiovascular status and risks of dementia were significant in *APOE* ε4 non-carriers but not in carriers in older adults with a mean age of 75 years.[27] In line with our findings, results from a previous study indicated that compared to *APOE* ε4 non-carriers, carriers had fewer declines in daily functioning, which is associated with multimorbidity[28] before dementia diagnosis.[29]

This study had some strengths. We compared patterns of TOM between natural aging and prodromal dementia based on a large, nationally representative cohort over a long period of 24 years. In addition, matched nested case–control design with a balanced distribution of age, sex, race, and education by dementia status was efficient in providing unbiased estimation.

There were several limitations in this study. First, although covering a long follow-up, the number of LTC was already significantly higher in dementia cases than in controls at the beginning of this study among females and individuals who were first identified as demented below 75 years old. As a result, assessments of multimorbidity at earlier adulthood were required to find the accurate beginning of diverged trajectory patterns. Second, participants were mainly White individuals, which precluded the generalizability of findings to other ethnicities. Third, dementia status was determined based on the self- or proxy-reported scores of TICS-m but not clinical diagnosis, which might lead to a bias of misclassification. Fourth, the burden of multimorbidity was self-reported and quantified with the counts of seven chronic conditions without consideration of other diseases (e.g., elevated cholesterol, chronic kidney disease, and infections) or the relative impact of each disease,[30] which might induce biases of recall and misclassification. Fifth, although 1752 of 2133 dementia cases were successfully matched to controls, estimations might be biased due to the loss of demented cases. Furthermore, laboratory experiments were warranted to elucidate potential biological mechanisms of modification effects found in subgroup analyses.

In conclusion, results of the present study suggested that the preclinical trajectory of increase in multimorbidity initiates at 20 years before dementia diagnosis, with modifications of age and sex. Our findings proposed the optimal time windows for multimorbidity intervention in dementia prevention.

AUTHOR CONTRIBUTIONS

Conceptualization: Jing Guo; data acquisition: Jing Guo, Suhang Song; data analysis: Jing Guo; data interpretation: Jing Guo; drafting manuscript: Jing Guo, Bin Gao, Yun Huang; revising manuscript: Suhang Song; approving final version of the manuscript: all authors.

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CONFLICT OF INTEREST STATEMENT

All authors declare no conflicts of interest. Author disclosures are available in the supporting information.

DATA AVAILABILITY STATEMENT

Date used in the present study are publicly available on the website of HRS (https://hrs.isr.umich.edu/about).

CONSENT STATEMENT

All participants provided informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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