Research Article

Multimorbidity and Cognitive Decline Over 14 Years in Older Americans

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Abstract

Background: Multimorbidity is associated with greater disability and accelerated declines in physical functioning over time in older adults. However, less is known about its effect on cognitive decline.

Methods: Participants without dementia from the Health and Retirement Study were interviewed about physician-diagnosed conditions, from which their multimorbidity-weighted index (MWI) that weights diseases to physical functioning was computed. We used linear mixed-effects models to examine the predictor MWI with the modified Telephone Interview for Cognitive Status (TICS_m, global cognition), 10-word immediate recall and delayed recall, and serial 7s outcomes biennially after adjusting for baseline cognition and covariates.

Results: Fourteen thousand two hundred sixty-five participants, 60% female, contributed 73,700 observations. Participants had a mean $\pm$ SD age 67 ± 9.3 years and MWI 4.4 ± 3.9 at baseline. Each point increase in MWI was associated with declines in global cognition (0.04, 95% CI: 0.03–0.04 TICS_m), immediate recall (0.01, 95% CI: 0.01–0.02 words), delayed recall (0.01, 95% CI: 0.01–0.02 words), and working memory (0.01, 95% CI: 0.01–0.02 serial 7s; all $p < .001$). Multimorbidity was associated with faster declines in global cognition (0.003 points/year faster, 95% CI: 0.002–0.004), immediate recall (0.001 words/year faster, 95% CI: 0.001–0.002), and working memory (0.006 incorrect serial 7s/year faster, 95% CI: 0.004–0.009; all $p < .001$), but not delayed recall compared with premorbid slopes.

Conclusions: Multimorbidity using a validated index weighted to physical functioning was associated with acute decline in cognition and accelerated and persistent cognitive decline over 14 years. This study supports an ongoing geriatric syndrome of coexisting physical and cognitive impairment in adults with multimorbidity. Clinicians should monitor and address both domains in older multimorbid adults.

Key words: Cognition, Cognitive aging, Functional performance, Multimorbidities

An increasing number of adults are living with multimorbidity, the coexistence of multiple chronic conditions (1). The rise in prevalence is partially attributed to population aging but also clinical, public health, and societal factors (2). Although improvements in early diagnosis and treatment of chronic conditions like cardiovascular disease and cancer have resulted in an increased average lifespan among those with multimorbidity (3), not all additional years are characterized by good functional health. In the United States, 16 million community-dwelling adults older than age 65 years live with a disability (4), and the prevalence of activity limitations in younger and middle-aged adults is increasing (5).

Multimorbidity is associated with higher rates of adverse outcomes including worse physical functioning, health-related quality of life, disability, and mortality (6–9). However, less is known about its association with cognitive functioning and rate of cognitive decline over time as multimorbidity persists or worsens. Multimorbidity has been associated with worse cognitive functioning, but prior studies used cross-sectional designs (10) or examined a simple disease count without considering the differential impacts that individual conditions have on functioning (10–12). Furthermore, prior studies have not accounted for baseline differences in cognitive function due to

multimorbidity so that causal links of incident multimorbidity on cognitive decline can be better identified and quantified.

A cross-sectional study examined physical conditions in 75- to 95-year-old adults and reported a dose-response association with mild cognitive impairment for ≥ 1 conditions versus none (13). Building on this, in community-dwelling adults ≥ 50 years from six low- and middle-income countries, increasing multimorbidity had a monotonic association with mild cognitive impairment (10). In longitudinal studies including the Baltimore Longitudinal Aging Study of Baltimore residents aged 65–95 years followed for an average of 3 years (12) and the Mayo Clinic Study of Aging of 70- to 89-year-old Minnesota residents followed for an average of 4 years (11), increasing multimorbidity was associated with risk of mild cognitive impairment. In the Baltimore Longitudinal Aging Study, faster disease accumulation was associated with significantly steeper rates of decline in verbal (categorical and letter) fluency but not global cognition, executive function, spatial ability, and memory (figural, verbal, attention, working). None of these prior studies controlled for baseline cognitive levels to better delineate incident multimorbidity with subsequent cognitive decline and rate of cognitive decline.

Basic, clinical, and epidemiological evidence has implicated a central nervous system role in physical functioning (eg mobility limitations) in older adults without clinical neurological disease (14). For example, gait requires executive functioning and attention and deteriorates during dual tasking (15). Therefore, there is growing interest in an emerging geriatric syndrome encompassed by concomitant declines in both cognitive and physical functioning. The presence of coexisting cognitive impairment and physical disability was associated with increased all-cause mortality in older men, but cognitive impairment without physical disability was not (16). Furthermore, physical activity has been shown to modify the association between multimorbidity and cognitive function (17). Multimorbidity may be a proxy for multisystem dysregulation, whereas physical functioning reflects the integrative impact of diseases that contribute to multimorbidity. It is thus reasonable to hypothesize linked associations between multimorbidity and both cognitive and physical functioning.

We sought to better characterize the association between incident multimorbidity and cognitive decline over several years in older adults by incorporating physical functioning. A validated multimorbidity-weighted index (MWI) (18) that weights chronic conditions to physical functioning would enable a unique assessment of multimorbidity and physical functioning in relation to cognitive functioning and rate of cognitive decline. Second, we aimed to compare the performance of MWI with a commonly used measure of multimorbidity, simple disease count, in predicting the future rate of cognitive decline.

Method

Study Population

The Health and Retirement Study (HRS) is a nationally representative population-based prospective cohort of U.S. adults ≥ 51 years old followed since 1992. Participants report on physician-diagnosed medical conditions, functional status, living situation, household income, and health behaviors (19). For our study, we included participants who completed at least one interview regarding physician-diagnosed chronic conditions, and ≥ 2 cognitive assessments between 2000 and 2014. We required baseline measurements for each cognitive outcome to control for baseline cognition. Participants with existing

multimorbidity at baseline were included, as we also sought to examine the association of persistent multimorbidity on cognitive functioning and decline over time. We excluded participants with baseline dementia defined as a modified Telephone Interview for Cognitive Status (TICSm) (20) score ≤ 6 (21) and respondents represented by a proxy (Supplementary Figure 1).

Cognitive Functioning Assessment

The primary outcome, global cognition, was assessed using TICSm (20), a global measure of cognition that includes orientation (day, month, year), 10-item immediate word recall and 10-item delayed word recall to assess memory, and serial 7s to assess information processing speed. TICSm (range 0–27) was administered at baseline and at each biennial follow-up wave with an average of 46% conducted face-to-face and 54% via phone.

Secondary outcomes included more specific cognitive domains, including episodic memory and working memory. We assessed episodic memory through immediate word recall and delayed word recall. The interviewer read one of four possible sets of 10 nouns, and respondents were asked to recall as many of the 10 words as possible immediately (range 0–10) and after 5 minutes (range 0–10) in any order.

To assess working memory, we used the serial 7s test (22). Participants were asked to subtract 7 five times, starting from 100. The interviewer added the correct subtractions (range 0–5), each independently scored so that correct subsequent subtractions counted regardless of a previous mistake. Participants who quit or refused to perform the test entirely were designated missing (22).

Multimorbidity Measurement

We measured multimorbidity using a validated MWI (7, 18). Briefly, chronic conditions were weighted by their association with the Short Form (SF)-36 physical functioning scale, then summed to form each individual's MWI. MWI represents both cumulative burden of chronic conditions and decreased physical functioning. An increase in MWI represents a worsening of multimorbidity and physical functioning. In this study, we applied our previously established weights to 16 self-reported conditions in HRS (myocardial infarction, angina, congestive heart failure, arrhythmia, other heart problems, stroke, hypertension, chronic lung disease, cancer excluding skin, diabetes, arthritis, connective tissue disease, hip/knee replacement, dementia, and glaucoma). MWI was a time-varying predictor updated biennially. We captured existing multimorbidity at baseline and incident multimorbidity over follow-up. MWI at each time point represents persistent conditions plus new burden of incident conditions. Simple disease count included the same conditions in MWI but conditions were unweighted.

Covariate Assessment

Using a prior cross-sectional study of multimorbidity and global cognition in HRS (7), we selected covariates considered as important predictors for multimorbidity and cognitive functioning, including age, sex, race/ethnicity, body mass index (BMI), smoking status, alcohol use, vigorous physical activity, education, household net worth, marital status/living arrangement, and time since baseline assessment. The following were assessed as time-varying covariates: BMI, alcohol use, physical activity, household net worth, and marital status/living arrangement. We also adjusted for baseline cognitive functioning for each respective cognitive outcome to control for cognition before incident multimorbidity or further progression.

We excluded 130 participants missing covariates: smoking status ($N = 97$), BMI ($N = 19$), alcohol use ($N = 10$), vigorous physical activity ($N = 3$), and race/ethnicity ($N = 1$). There were no significant differences by MWI or cognitive functioning at baseline between included and excluded participants (Supplementary Table 1).

Statistical Analysis

We fit linear mixed-effects models with an unstructured covariance matrix and random intercept and random slope to examine the association between time-varying incident multimorbidity with changes in global cognition and individual cognitive domains including immediate recall, delayed recall, and serial 7s. Multilevel modeling is appropriate for repeated measures to describe yearly decline in cognition and the impact of time-varying multimorbidity on this decline. We used a 2 year lagged period between multimorbidity and subsequent cognitive assessments. MWI and all outcomes were measured continuously to more precisely estimate changes in cognitive function between participants.

Time was expressed as years since baseline. Model 1 included time-varying MWI to estimate the effect of each one-point increase in MWI on the acute decline in cognitive function at the time of acquiring new chronic conditions. This variable indicates the “acute decline in cognitive function (change in intercept) associated with the participant’s burden of incident chronic conditions.” Model 2 included Model 1 variables plus time after multimorbidity to estimate the effect of multimorbidity on the “decline in cognitive function over the years following the event (change in slope).” We adjusted for all covariates and baseline cognitive functioning for each respective cognitive outcome, which is a potential over-adjustment in the case of preclinical disease, but superior to measuring change scores over time (23).

For all cognitive outcomes, we examined potential interactions between MWI and years since baseline. For statistically significant interactions, we included the interaction term in the final model. To illustrate the effect of significant interactions between MWI and time on the slope (vs. no interaction with time), we calculated participant-specific (conditional) predicted values for each cognitive score for an exemplary participant with the mean age and covariates (Supplementary Figure 2). We also modeled the effect of worsening MWI (ie current multimorbidity plus incident conditions) over time, compared with constant MWI (ie current multimorbidity without incident conditions) over time, on cognitive outcomes for the same exemplary participant.

Last, we compared the model fit measuring multimorbidity with standardized MWI versus simple disease count for all cognitive outcomes through the Akaike Information Criterion (AIC). For another comparison, we included both MWI and disease count concurrently in the model. By adjusting for disease count, we examined the effect of MWI disease weights on each outcome. For all analyses, statistical significance was set as $p < .05$ (2-sided) and performed using STATA, version 14.2 (StataCorp, College Station, TX, 2015).

Results

Participant Characteristics

At baseline, 18,612 cohort-eligible adults participated in the 2000 interview. The final sample included 14,265 (77%) participants who contributed 73,700 observations over a mean $\pm$ SD of 11 ± 4.2 years.

We excluded those with a TICSm ≤ 6 that would be categorized as dementia, proxy representation, no follow-up, and missing covariates (Supplementary Figure 1). At baseline, participants had mean age 66.6 ± 9.1 years, MWI 4.4 ± 3.9 , TICSm score 15.9 ± 4.1 , immediate recall 5.7 ± 1.6 words, delayed recall 4.6 ± 2.0 words, and serial 7s 3.6 ± 1.6 (Table 1).

Table 1. Participant Characteristics at Baseline, 2000

Characteristic	Health and Retirement Study N = 14,265		
	No. (%)	Mean	Standard deviation
Age, yr		66.6	9.1
Sex, female	8,563 (60.0)		
Race			
White	11,280 (79.1)		
Black	1,741 (12.2)		
Hispanic	995 (7.0)		
Other	249 (1.8)		
Body mass index, kg/m ²		27.4	5.3
<18.5	193 (1.4)		
18.5–24.9	4,681 (32.8)		
25–29.9	5,753 (40.3)		
≥ 30	3,638 (25.5)		
Smoking status			
Never smoker	5,896 (41.3)		
Past smoker	6,248 (43.8)		
Current smoker	2,121 (14.9)		
Alcohol use			
Never	7,369 (51.7)		
Former	2,782 (19.5)		
1 per week	1,137 (8.0)		
>1 per week	2,977 (20.9)		
Vigorous physical activity	6,529 (45.8)		
≥ 1 per week			
Education, yr		12.4	3.1
<12	3,437 (24.1)		
12	5,093 (35.7)		
13–15	2,841 (19.9)		
≥ 16	2,894 (20.3)		
Household net worth, \$		312,266	940,593
$\leq 14,000$	1,949 (13.7)		
14,001–113,000	4,554 (31.9)		
113,001–323,700	4,328 (30.3)		
$\geq 323,701$	3,434 (24.1)		
Living arrangement			
Married or living with partner	9,599 (67.3)		
Living with someone other than partner	1,457 (10.2)		
Living alone	3,209 (22.5)		
Multimorbidity-weighted index, 0–37		4.4	3.9
Number of chronic conditions, 0–12		1.7	1.3
Cognitive status, Telephone Interview for Cognitive Status-modified, 0–27		15.9	4.1
Normal, 12–27	11,996 (64.1)		
Cognitive Impairment	2,269 (15.9)		
No Dementia, 7–11			
Immediate recall, 0–10 words		5.7	1.6
Delayed recall, 0–10 words		4.6	2.0
Serial 7s, 0–5		3.6	1.6

Multimorbidity and Global Cognition

Each one-point increase in MWI was associated with an acute decline in global cognition after the event (-0.08 TICSm score, 95% CI: -0.09 , -0.07) in model 1 without the multimorbidity–time interaction. This attenuated to -0.034 TICSm (95% CI: -0.043 , -0.029) after adjustment for all covariates including baseline cognitive functioning. After adding the multimorbidity–time interaction in model 2, the association attenuated but persisted (Table 2). The acute effect of a one-point increase in MWI on global cognition was equal to the effect of 0.33 years of aging on global cognition in the same individual in adjusted models. As a sensitivity analysis, we present model 2 without adjustment for baseline cognition, to show the effect of baseline cognition on the association between MWI and cognitive decline (Supplementary Table 2).

MWI was also associated with faster rates of decline in global cognition over time (-0.003 , 95% CI: -0.005 , -0.002 lower TICSm/year faster; Table 2). As illustrated in Supplementary Figure 2 featuring adjusted models including baseline cognitive functioning and the interaction between multimorbidity and time, an exemplary HRS participant with worsening MWI experienced a faster rate of decline in global cognition. For example, a participant who accumulated chronic conditions with an increase in MWI of 3 points every 4 years for 8 years (MWI = 8 at year 4, MWI = 11 at year 8) and 3 points MWI after 10 years from baseline (MWI = 14 at year 10) had a 3-point lower predicted TICSm than that of an average HRS participant whose MWI remained constant at 5 over the same period.

Multimorbidity and Memory

Each one-point increase in MWI was associated with acute declines in immediate recall (-0.014 , 95% CI: -0.016 , -0.011 words) and delayed recall (-0.014 , 95% CI: -0.018 , -0.011 words) in model 1 (both $p < .001$; Table 2). The effect of a one-point increase in MWI on each immediate and delayed memory was approximately equal to the effect of 0.2 years of aging in the same individual in adjusted models. These associations mildly attenuated but persisted after including the multimorbidity–time interaction (model 2, Table 2). Model 2 without adjustment for baseline cognition was included to demonstrate the effect of baseline cognition on the association between MWI and cognition decline (Supplementary Table 2).

Each one-point increase in MWI was also associated with faster declines in immediate recall over time (-0.001 , 95% CI: -0.002 , -0.001 fewer words/year faster) but not in delayed recall (Table 2). The faster rate of decline in immediate and delayed memory for worsening MWI in an average HRS participant is illustrated in Supplementary Figure 2. A participant whose MWI increased 3 points every 4 years for 8 years (MWI = 8 at year 4, MWI = 11 at year 8) and 3 points at year 10 from baseline (MWI = 14 at year 10) had a predicted immediate recall that was 1 word lower than that of an average HRS participant whose MWI remained constant at 5 over the same period.

For working memory, each one-point increase in MWI was associated with an acute decline in serial 7s over time (0.009 , 95% CI: 0.007 – 0.0012 fewer subtractions) in model 1 (Table 2). MWI was also associated with faster rates of decline in serial 7s over time (0.001 , 95% CI: 0.001 – 0.002 fewer serial 7s/year faster; model 2, Table 2), similar to the model without adjustment for baseline cognition (Supplementary Table 2).

MWI Versus Simple Disease Count

MWI captured a broader distribution of multimorbidity than simple disease count particularly at high values (MWI range 0–37, disease count range 0–12). As an expansive continuous measure, MWI provided more unique values to precisely quantify multimorbidity than limited integer values of disease count.

MWI had greater magnitudes of association than disease count by 22% for TICSm, 11% for immediate recall, and no difference for delayed recall. MWI was associated with a 10% faster rate of decline in TICSm and 29% faster rate of decline in serial 7s than disease count, and there were no differences for rate of decline in immediate and delayed recall. MWI was more parsimonious than disease count for all cognitive outcomes based on lowest AIC (Table 3).

Finally, in direct comparisons with collinear predictors MWI and disease count competing in the same model, the association between MWI and each cognitive outcome persisted while the associations with disease count did not (Table 4). For global cognition, the association between MWI and TICSm was -0.29 (95% CI: -0.04 , -0.02), whereas the association between disease count and TICSm was nonsignificant (-0.02 , 95% CI: -0.07 , 0.02).

Discussion

In this large nationally representative cohort of U.S. adults, multimorbidity using a validated MWI was associated with accelerated and persistent rates of decline in global cognition and verbal memory over time, controlling for each participant's pre-morbid cognitive level. We also demonstrated that MWI provides a wider distribution and more unique values to precisely characterize multimorbidity in participants, and greater parsimony for predicting cognitive functioning and rate of decline than simple disease count.

This study extends prior studies of multimorbidity and cognitive functioning. Previous studies have reported an association between cognitive impairment and multimorbidity but examined multimorbidity as a count of chronic conditions instead of allowing conditions to have differential impacts on physical functioning and hence also cognitive functioning (10–13). Compared with prior studies, ours had the longest follow-up (14 years) and examined rate of cognitive decline with baseline and incident multimorbidity after robust adjustment for time-varying covariates and baseline cognitive functioning. Furthermore, we assessed multimorbidity through a validated MWI rather than disease count or traditional metrics weighted to mortality. Although conditions in MWI were specifically weighted to physical functioning, MWI was nonetheless associated with an acute decline (change in intercept) and faster rates of decline (change in slope) in cognitive functioning as assessed through global cognition, immediate and delayed recall, and working memory.

Finally, in addition to global cognition, we examined specific cognitive domains. Specifically, multimorbidity appears to be detrimental for episodic memory and working memory, which are particularly sensitive to neurodegenerative disease. Compared with memory retrieval (delayed recall), which was marginally statistically significant, learning (immediate recall) may place greater demands on frontal lobe processes, including attention, working memory, and executive functioning. These processes may be more vulnerable to the vascular effects of chronic diseases than those mediated more by temporal lobe structures. Hence, multimorbidity is more likely to influence frontal lobe functions (12).

Our study has limitations. First, MWI was limited to only 16 chronic conditions based on assessed conditions in HRS and is likely

Table 2. Adjusted Changes and 95% CIs in Predicted Global Cognitive Functioning, Delayed and Immediate Word Recall, and Working Memory With Incident Multimorbidity for Each 1-Point Increase in the Multimorbidity-Weighted Index, 2000–2014

	TICSm				Delayed word recall				Immediate word recall				Serial 7s test			
	Model 1		Model 2		Model 1		Model 2		Model 1		Model 2		Model 1		Model 2	
	Regression coefficient (95% CI)	p-value	Regression coefficient (95% CI)	p-value	Regression coefficient (95% CI)	p-value	Regression coefficient (95% CI)	p-value	Regression coefficient (95% CI)	p-value	Regression coefficient (95% CI)	p-value	Regression coefficient (95% CI)	p-value	Regression coefficient (95% CI)	p-value
Time	–0.21 (–0.21, –0.20) $p < .001$		–0.18 (–0.20, –0.18) $p < .001$		–0.08 (–0.09, –0.08) $p < .001$		–0.08 (–0.08, –0.08) $p < .001$		–0.07 (–0.08, –0.07) $p < .001$		–0.05 (–0.07, –0.06) $p < .001$		–0.03 (–0.03, –0.03) $p < .001$		–0.03 (–0.03, –0.02) $p < .001$	
Multimorbidity-weighted index	–0.034 (–0.043, –0.029) $p < .001$		–0.015 (–0.025, –0.006) $p = .002$		–0.014 (–0.018, –0.011) $p < .001$		–0.011 (–0.016, –0.006) $p < .001$		–0.014 (–0.016, –0.011) $p < .001$		–0.006 (–0.010, –0.002) $p = .002$		–0.009 (–0.012, –0.007) $p < .001$		–0.002 (–0.006, 0.002) $p = .36$	
MWI * Time	N/A		–0.003 (–0.004, –0.002) $p < .001$		N/A		–0.001 (–0.001, 0.000) $p = .06$		N/A		–0.001 (–0.002, –0.001) $p < .001$		N/A		–0.001 (–0.002, –0.001) $p < .001$	
Age	–0.13 (–0.13, –0.12) $p < .001$		–0.13 (–0.13, –0.12) $p < .001$		–0.07 (–0.07, –0.07) $p < .001$		–0.07 (–0.07, –0.07) $p < .001$		–0.06 (–0.06, –0.05) $p < .001$		–0.06 (–0.06, –0.05) $p < .001$		–0.02 (–0.02, –0.01) $p < .001$		–0.02 (–0.02, –0.02) $p < .001$	
Intercept	15.08 (14.64, 15.53) $p < .001$		15.02 (14.58, 15.47) $p < .001$		6.71 (6.52, 6.91) $p < .001$		6.71 (6.51, 6.90) $p < .001$		6.71 (6.54, 6.88) $p < .001$		6.69 (6.52, 6.86) $p < .001$		2.63 (2.47, 2.78) $p < .001$		2.61 (2.46, 2.76) $p < .001$	
Log likelihood	–186536.1		–186518.4		–137414.5		–137412.7		–124727.5		–124716.2		–117160.6		–117146.7	

Notes: N = 14,265 participants, $n = 73,700$ observations.

CI = confidence interval; MWI = multimorbidity-weighted index; N/A = not applicable; TICSm = Telephone Interview for Cognitive Status, modified.

Model 1: MWI, covariates (age (years), sex, race/ethnicity (white, black, Hispanic, other), education (<12, 12, 13–15, ≥16 years, household net wealth (≤\$14,000, \$14,001–\$113,000, \$113,001–\$323,700, ≥\$323,701), marital status/living arrangement (married or living with partner, living with someone other than partner, living alone), BMI (<18.5, 18.5–24.9, 25–29.9, ≥30 kg/m², smoking status (never, past, current), alcohol use (never, former, 1 drink/week, >1 drink/week), physical activity (≥1 vigorous physical activity/week), years since baseline), respective cognitive functioning measure at baseline.

Model 2: additionally adjusted for interaction between MWI and time.

Table 3. Comparison Between the Standardized Multimorbidity-Weighted Index and Simple Disease Count for Multimorbidity and Adjusted Changes in Global Cognitive Functioning, Delayed and Immediate Word Recall, and Working Memory, Health and Retirement Study, 2000–2014

	TICS _m		Delayed word recall		Immediate word recall		Serial 7s test	
	MWI Regression coefficient (95% CI) p-value	Disease count Regression coefficient (95% CI) p-value	MWI Regression coefficient (95% CI) p-value	Disease count Regression coefficient (95% CI) p-value	MWI Regression coefficient (95% CI) p-value	Disease count Regression coefficient (95% CI) p-value	MWI Regression coefficient (95% CI) p-value	Disease count Regression coefficient (95% CI) p-value
Time	–0.18 (–0.20, –0.18) <i>p</i> < .001	–0.18 (–0.19, –0.17) <i>p</i> < .001	–0.08 (–0.08, –0.08) <i>p</i> < .001	–0.08 (–0.08, –0.07) <i>p</i> < .001	–0.06 (–0.07, –0.06) <i>p</i> < .001	–0.06 (–0.07, –0.06) <i>p</i> < .001	–0.03 (–0.03, –0.02) <i>p</i> < .001	–0.02 (–0.03, –0.02) <i>p</i> < .001
Multimorbidity- Weighted Index	–0.083 (–0.135, –0.031) <i>p</i> = .002	N/A	–0.060 (–0.086, –0.033) <i>p</i> < .001	N/A	–0.035 (–0.057, –0.013) <i>p</i> = .002	N/A	–0.002 (–0.006, 0.002) <i>p</i> = .36	N/A
MWI * Time	–0.018 (–0.024, –0.012) <i>p</i> < .001	N/A	–0.003 (–0.010, 0.000) <i>p</i> = .06	N/A	–0.006 (–0.009, –0.004) <i>p</i> < .001	N/A	–0.001 (–0.002, –0.001) <i>p</i> < .001	N/A
Disease count	N/A	–0.068 (–0.120, –0.016) <i>p</i> = .01	N/A	–0.060 (–0.085, –0.033) <i>p</i> < .001	N/A	–0.031 (–0.053, –0.010) <i>p</i> = .004	N/A	–0.001 (–0.021, 0.019) <i>p</i> = .92
Disease count*Time	N/A	–0.020 (–0.026, –0.014) <i>p</i> < .001	N/A	–0.003 (–0.006, –0.000) <i>p</i> = .03	N/A	–0.006 (–0.009, –0.004) <i>p</i> < .001	N/A	–0.007 (–0.009, –0.005) <i>p</i> < .001
Age	–0.13 (–0.13, –0.12) <i>p</i> < .001	–0.13 (–0.13, –0.12) <i>p</i> < .001	–0.07 (–0.07, –0.07) <i>p</i> < .001	–0.07 (–0.07, –0.06) <i>p</i> < .001	–0.06 (–0.06, –0.05) <i>p</i> < .001	–0.06 (–0.06, –0.05) <i>p</i> < .001	–0.02 (–0.02, –0.02) <i>p</i> < .001	–0.02 (–0.02, –0.02) <i>p</i> < .001
Intercept	15.02 (14.58, 15.48) <i>p</i> < .001	14.98 (14.53, 15.42) <i>p</i> < .001	6.71 (6.51, 6.90) <i>p</i> < .001	6.69 (6.49, 6.89) <i>p</i> < .001	6.69 (6.52, 6.86) <i>p</i> < .001	6.67 (6.51, 6.84) <i>p</i> < .001	2.61 (2.46, 2.76) <i>p</i> < .001	2.60 (2.45, 2.75) <i>p</i> < .001
Log likelihood	–186518.3	–186522.6	–137412.7	137413.7	–124716.2	–124725.3	–117146.7	–117147.0
AIC	373098.8	373107.2	274887.4	274889.4	249494.3	249512.5	234355.3	234356.0

Notes: *N* = 14,265 participants, *n* = 73,700 observations.

AIC = Akaike Information Criterion; CI = confidence interval; MWI = multimorbidity-weighted index; N/A = not applicable; TICS_m = Telephone Interview for Cognitive Status, modified.

Adjusted for age, sex, race/ethnicity, education, household net wealth, marital status/living arrangement, BMI, smoking status, alcohol use, physical activity, years since baseline, respective cognitive functioning measure at baseline, and interaction between multimorbidity metric and time

an underestimate of multimorbidity. Finite inventories are a common limitation in national surveys and not unique to HRS. Nonetheless, assessed conditions were prevalent, spanned multiple organ systems, and were highly associated with physical functioning. Second, cognitive functioning was measured using validated global and specific measures commonly used for screening, but more comprehensive assessments would provide more sensitive estimates of cognitive functioning. Hearing loss could also limit cognitive assessment in person or via phone.

Finally, dementia is often underdiagnosed and underreported and likely also in HRS. We excluded participants with probable dementia based on the TICS_m at baseline, used a 2 year lag between diagnosis and cognitive functioning outcomes, and controlled for premorbid cognitive functioning to minimize reverse-causation. However, individuals who developed dementia during follow-up but who did not receive or report a formal physician-based diagnosis would have an

underestimated MWI. Our results may also underreport cognitive decline due to the inability to capture participants whose decline began prior to baseline. Because our study focused on change in cognitive function, participants must have had ≥2 cognitive assessments for study inclusion. The exclusion of participants with 1 observation meant that our assessed sample had a higher TICS_m score at baseline. It is thus possible that our results underreport cognitive decline as the sickest individuals who already experienced cognitive decline at an earlier date were not captured. This would bias to null the association between multimorbidity and cognitive functioning and decline.

This study has several clinical, research, and policy implications. Our results likely represent a clinically meaningful decline in cognitive functioning, whereby a single point increase in incident MWI was equivalent to the impact of 0.33 years of aging on global cognition, and 0.20 years of aging on immediate and delayed memory.

Table 4. Comparison Between the Multimorbidity-Weighted Index and Simple Disease Count Simultaneously in the Same Model for Adjusted Changes in Global Cognitive Functioning, Delayed and Immediate Word Recall, and Working Memory, Health and Retirement Study, 2000–2014

	TICS _m		Delayed word recall		Immediate word recall		Serial 7s test	
	Regression coefficient (95% CI)	p-Value	Regression coefficient (95% CI)	p-Value	Regression coefficient (95% CI)	p-Value	Regression coefficient (95% CI)	p-Value
Multimorbidity-weighted index, standardized	−0.15 (−0.23, −0.08)	<.001	−0.05 (−0.08, −0.01)	.007	−0.06 (−0.09, −0.04)	<.001	−0.05 (−0.07, −0.02)	.001
Disease count, standardized	−0.05 (−0.12, 0.26)	0.20	−0.04 (−0.07, 0.001)	0.04	−0.01 (−0.04, 0.02)	0.44	−0.004 (−0.03, 0.02)	0.77

Notes: $N = 14,265$ participants, $n = 73,700$ observations.

CI = confidence interval; TICS_m = Telephone Interview for Cognitive Status, modified.

Adjusted for age, sex, race/ethnicity, education, household net wealth, marital status/living arrangement, BMI, smoking status, alcohol use, physical activity, years since baseline, and respective cognitive functioning measure at baseline.

The magnitude of decline and rate of decline for global cognition and immediate and delayed memory exceeded by several fold the threshold of a change of 0.5 *SD* or greater using a common approach to define clinically meaningful change in cognitive functioning (24). This study identifies an existing and worsening geriatric syndrome characterized by concurrent declines in physical and cognitive functioning. Multimorbidity serves as a marker for cumulative disease burden and multiorgan system dysregulation manifesting in functional limitations and is a useful measure to assess this geriatric syndrome. Preventing the onset and progression of multimorbidity, which includes vascular conditions and risk factors for dementia, may be one potential strategy to decrease dementia risk. Although no effective dementia treatments exist currently, multidomain behavioral interventions may reduce the risk for cognitive decline among high-risk adults (25).

In summary, multimorbidity measured using a validated and readily accessible index weighted to physical functioning was independently associated with acute decline in cognitive functioning and also faster and persistent rates of cognitive decline over time among middle-aged and older adults. MWI provided a better model fit than a simple disease count for all cognitive outcomes. This study identifies an ongoing geriatric syndrome of coexisting physical and cognitive impairment in adults with multimorbidity. Clinicians should assess for and address both domains of functioning in older multimorbid adults.

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

None declared.

References

- Goodman RA, Posner SF, Huang ES, Parekh AK, Koh HK. Defining and measuring chronic conditions: imperatives for research, policy, program, and practice. *Prev Chronic Dis*. 2013;10:E66. doi:10.5888/pcd10.120239
- van Oostrom SH, Gijzen R, Stirbu I, et al. Time trends in prevalence of chronic diseases and multimorbidity not only due to aging: data from general practices and health surveys. *PLoS One*. 2016;11:e0160264. doi:10.1371/journal.pone.0160264
- DuGoff EH, Canudas-Romo V, Buttorff C, Leff B, Anderson GF. Multiple chronic conditions and life expectancy: a life table analysis. *Med Care*. 2014;52:688–694. doi:10.1097/MLR.0000000000000166
- Freedman V. The demography of late life disability. In: Hayward M, Majumdar MK, eds. *Future Directions for the Demography of Aging*. Washington, D.C.: National Academies Press; 2018. doi:10.17226/25064
- Martin LG, Schoeni RF. Trends in disability and related chronic conditions among the forty-and-over population: 1997–2010. *Disability and Health Journal*. 2014;7 (1 Suppl):S4–S14. doi:10.1016/j.dhjo.2013.06.007
- Wei MY, Mukamal KJ. Multimorbidity, mortality, and long-term physical functioning in 3 prospective cohorts of community-dwelling adults. *Am J Epidemiol*. 2018;187:103–112. doi:10.1093/aje/kwx198
- Wei MY, Kabeto MU, Langa KM, Mukamal KJ. Multimorbidity and physical and cognitive function: performance of a new multimorbidity-weighted index. *J Gerontol A Biol Sci Med Sci*. 2018;73:225–232. doi:10.1093/gerona/glx114
- Wei MY, Kabeto MU, Galecki AT, Langa KM. Physical functioning decline and mortality in older adults with multimorbidity: joint modeling of longitudinal and survival data. *J Gerontol A Biol Sci Med Sci*. 2018;74:226–232. doi:10.1093/gerona/gly038

9. Wei MY, Mukamal KJ. Multimorbidity and mental health-related quality of life and risk of completed suicide. *J Am Geriatr Soc.* 2019;67:511–519. doi:10.1111/jgs.15678
10. Koyanagi A, Lara E, Stubbs B, et al. Chronic physical conditions, multimorbidity, and mild cognitive impairment in low- and middle-income countries. *J Am Geriatr Soc.* 2018;66:721–727. doi:10.1111/jgs.15288
11. Vassilaki M, Aakre JA, Cha RH, et al. Multimorbidity and risk of mild cognitive impairment. *J Am Geriatr Soc.* 2015;63:1783–1790. doi:10.1111/jgs.13612
12. Fabbri E, An Y, Zoli M, et al. Association between accelerated multimorbidity and age-related cognitive decline in older Baltimore Longitudinal Study of Aging Participants without dementia. *J Am Geriatr Soc.* 2016;64:965–972. doi:10.1111/jgs.14092
13. Frisoni GB, Fratiglioni L, Fastbom J, Guo Z, Viitanen M, Winblad B. Mild cognitive impairment in the population and physical health: data on 1,435 individuals aged 75 to 95. *J Gerontol A Biol Sci Med Sci.* 2000;55:M322–M328. doi:10.1093/gerona/55.6.m322
14. Rosso AL, Studenski SA, Chen WG, et al. Aging, the central nervous system, and mobility. *J Gerontol A Biol Sci Med Sci.* 2013;68:1379–1386. doi:10.1093/gerona/glt089
15. Yogev-Seligmann G, Hausdorff JM, Giladi N. The role of executive function and attention in gait. *Mov Disord.* 2008;23:329–42; quiz 472. doi:10.1002/mds.21720
16. Yu WC, Chou MY, Peng LN, Lin YT, Liang CK, Chen LK. Synergistic effects of cognitive impairment on physical disability in all-cause mortality among men aged 80 years and over: results from longitudinal older veterans study. *PLoS One.* 2017;12:e0181741. doi:10.1371/journal.pone.0181741
17. Loprinzi PD. Multimorbidity, cognitive function, and physical activity. *Age (Dordrecht, Netherlands).* 2016;38(1):8. doi:10.1007/s11357-016-9874-5
18. Wei MY, Kawachi I, Okereke OI, Mukamal KJ. Diverse cumulative impact of chronic diseases on physical health-related quality of life: implications for a measure of multimorbidity. *Am J Epidemiol.* 2016;184:357–365. doi:10.1093/aje/kwv456
19. Sonnega A, Faul JD, Ofstedal MB, Langa KM, Phillips JW, Weir DR. Cohort profile: the Health and Retirement Study (HRS). *Int J Epidemiol.* 2014;43:576–585. doi:10.1093/ije/dyu067
20. Breitner JC, Welsh KA, Gau BA, et al. Alzheimer's disease in the National Academy of Sciences-National Research Council Registry of Aging Twin Veterans. III. Detection of cases, longitudinal results, and observations on twin concordance. *Arch Neurol.* 1995;52:763–771. doi:10.1001/archneur.1995.00540320035011
21. Crimmins EM, Kim JK, Langa KM, Weir DR. Assessment of cognition using surveys and neuropsychological assessment: the Health and Retirement Study and the Aging, Demographics, and Memory Study. *J Gerontol B Psychol Sci Soc Sci.* 2011;66 (Suppl 1):i162–i171. doi:10.1093/geronb/gbr048
22. Ofstedal MB, Fisher GG, Herzog AR. *Documentation of Cognitive Functioning Measures in the Health and Retirement Study.* Ann Arbor, MI: University of Michigan Survey Research Center; 2005. doi:10.7826/isr-um.06.585031.001.05.0010.2005
23. Vickers AJ, Altman DG. Statistics notes: analysing controlled trials with baseline and follow up measurements. *BMJ.* 2001;323:1123–1124. doi:10.1136/bmj.323.7321.1123
24. Stein J, Luppia M, Maier W, et al. The assessment of changes in cognitive functioning in the elderly: age- and education-specific reliable change indices for the SIDAM. *Dement Geriatr Cogn Disord.* 2012;33(2–3):73–83. doi:10.1159/000336864
25. Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet.* 2015;385:2255–2263. doi:10.1016/S0140-6736(15)60461-5