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Multiple Chronic Conditions: implications for cognition - findings from the Wisconsin Registry for Alzheimer's Prevention (WRAP)

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Abstract

INTRODUCTION: Several chronic illnesses have demonstrated relationships to cognitive decline in the context of aging. However, researchers have largely ignored the effects of multi-morbidity in the context of Alzheimer's disease and related dementias (ADRD) risk. The purpose of this study is to examine the relationship between multiple chronic conditions (MCC) and cognitive decline.

METHODS: Latent class analysis (LCA) was completed to identify different subgroups of the 1,285 participants from the Wisconsin Registry for Alzheimer's Prevention who were recognized based on their self-reported chronic illnesses. Differences between variables of interest (*i.e.*, biomarkers and depressive symptom scores) and each of the individual classes were then explored. Chi-square tests were used to examine the association between MCC and cognitive status.

RESULTS: LCA revealed a four-class model best fit solution. Participants in the sleep class had the highest incidence of new onset cognitive decline.

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Conflicts
None

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DISCUSSION: Findings offer evidence of an association between specific MCC groups and the development of cognitive decline. Nurses should monitor and screen for cognitive decline in the presence of MCC in order to better target self-management

Keywords

Multiple chronic conditions; cognition; Alzheimer's risk; latent class analysis; Alzheimer's prevention

1. Background

Alzheimer's disease is the 6th leading cause of death and the only leading cause of death whose prevalence continues to grow [1]. Further, it is the only leading cause of death for which there is no prevention, no treatment and no cure. According to the Alzheimer's Association, in 2017, Alzheimer's disease and other related dementias (ADRD) accumulated more than \$259 billion in health care and related costs and this cost is expected to rise to an estimated \$1.1 trillion by 2050. To date, the literature has explored risk factors for ADRD that included age, family history, genetics (ApoE), sex, cardiovascular conditions and lifestyle variables such as diet and exercise. Several chronic illnesses have demonstrated relationships to cognitive decline [2–6], but researchers have largely ignored the effects of multi-morbidity on cognition and risk of ADRD. Multiple chronic illnesses (MCC) are the presence of two or more chronic illnesses and according to recent US Centers for Disease Control and Prevention statistics, three out of four adults over the age of 65 suffer from MCC [1]. Multiple chronic conditions are associated with poor outcomes such as greater disability, increased risk of hospitalization, decreased physical function, diminished quality of life and increased mortality [7–11]. Given that the incidence of MCC rise as the population ages, it seems crucial that nurse scientists explore MCC within the context of ADRD. Multiple chronic conditions may obfuscate or may mimic the early symptomology of ADRD and may represent a risk factor for cognitive decline that is amenable to nursing intervention. Therefore, the purpose of this study is to examine the relationship between MCC and cognitive decline in the Wisconsin Registry for Alzheimer's Prevention (WRAP), a longitudinal observational cohort enriched for Alzheimer's disease risk with multiple waves of cognitive assessment. We hypothesized that cognitive status would differ between the *chronic illness* subgroups.

2. Methods

2.1 Sample

This study is an analysis of existing longitudinal data derived from the WRAP. Details regarding enrollment and data collection for this registry have been previously published [12, 13]. In brief, WRAP participants are predominantly (73%) adult biological children of persons with Alzheimer's Disease (AD), either confirmed by autopsy or deemed probable as defined by the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association research criteria [14]. WRAP also enrolls healthy controls with no parental history of AD or dementia. For this study, both groups were used in the analysis. Subjects were English-speaking and 36 to 68 years of age

and cognitively intact at the time of enrollment. Rolling enrollment for WRAP began in November 2001 and continues.

2.2 Study Procedures

WRAP data are collected at the baseline (visit 1), at approximately 4 years' postbaseline (visit 2), and then every 2 years (visits 3 and following) thereafter. For this study, *all participants with complete data of interest (i.e., cognitive, biomarker and self-report questionnaires) were included in the analysis. Based on this criteria, we were able to capture participants across 4 visit time points* (spanning approximately 8 years). Specially, data related to demographic characteristics were collected at visit 1, data pertaining to MCC were collected at visits 1 through 3, and the corresponding data related to cognitive functioning was collected at visits 1 through 4, for all participants who had MCC data at visit 3. The total number of participants meeting inclusion for this study was 1,285. All study procedures were approved by the University of Wisconsin-Madison Health Sciences Institutional Review Board.

2.3 Instruments

2.3.1 Health History Questionnaire—A health-history questionnaire derived from the National Institutes of Health (NIH) Women's Health Initiative Memory Study was used to collect self-reported demographic data, health-related lifestyle behaviors (smoking, alcohol intake, exercise), current medications and medical history. To collect medical history data, participants were given a list of over 40 common conditions and asked if they had ever been diagnosed or told by a health care provider that they had the condition. Possible responses were "yes, no, or don't know". The 20-item Center for Epidemiologic Studies-Depression scale [CES-D] was used to collect depressive symptoms [15].

2.3.2 Neuropsychological Tests—A battery of commonly used cognitive tests was administered at baseline and at each subsequent visit. See Sager *et. at.*, 2005 for a detailed description of these procedures. *Cognitive tests administered at visits 1 through 4 were used for this analysis and included measures of multiple cognitive domains including verbal episodic learning and memory, working memory, and executive function. Following each visit, memory and executive function factor scores are compared to robust cohort norms which account for the relatively young age and high education level of the cohort; these robust norms are more sensitive to subtle, preclinical decline than are published norms. Information about the WRAP robust factor score norms has been published previously [17], but briefly, after adjusting for age, sex, and literacy (as measured by the Wide Range Achievement Test reading recognition), factor scores that fall below the threshold of -1.5 SD from the group mean are considered impaired. Participants are classified as either psychometric amnesic mild cognitive impairment (aMCI) if memory factor scores were below threshold or psychometric non-amnesic mild cognitive impairment (naMCI) if executive function factor scores were below threshold. For this analysis, participants were labeled as aMCI if they had at least two visits with aMCI as described and naMCI if they had at least two visits with naMCI. Labeling aMCI and/or naMCI based on two or more visits reduces the potential false positive rate and provides a more accurate picture of cognition among the sample.*

2.4 Analysis

We used Mplus Version 7.4 (Muthen and Muthen, 2016) to conduct a Latent Class Analysis (LCA), to identify different subgroups of patients who were recognized based on their self-reported chronic illnesses. Basically, LCA allows one to detect homogenous subgroups in a heterogenous group through evaluating and then minimizing associations among responses across a set of indicators. To determine the number of classes, we used the following selection criteria: (1) interpretability; (2) theoretical justification; (3) parsimony; (4) lowest adjusted Bayesian Information Criteria (BICa) score; (5) lowest CAIC; (6) Entropy>0.7; (7) average posterior probability in each class >0.75 and no more than 10% overlap/cross-membership between non-contiguous classes; (8) at least 2.5% of total count in each group; and (9) no significant improvement as assessed by likelihood ratio test (Lo-Mendall-Rubin) [18, 19],

We were interested in validating the latent classes using observed biomarkers. While different approaches have been proposed for this auxiliary analysis, we used the BCH method [24–26]. BCH explores differences in the variables of interest (*i.e.*, biomarkers) and each of the individual classes. For this study, we chose several biometric health indicators (Interluken-6 (IL-6), high sensitivity C-reactive protein (hs- CRP), fasting blood glucose, and body mass index (BMI)) and depression scores based on their association with specific chronic illnesses.

Examination of association between multi-morbidity classes and cognitive status was conducted using Chi-square test.

3. Results

3.1 Demographic Characteristics

The sample was predominantly female and Caucasian, with a mean age of 54 years old (SD 7). Other demographic characteristics are found in Table 1. One-hundred and fifty-eight participants were classified as psychometric aMCI and 85 participants were classified as psychometric naMCI.

3.2 Latent class analysis - four class solution

In general, we see support for a four-class solution, that included 14 of the 40 chronic illnesses (Figure 1). The four-class solution provided at most only 5% overlap, which was less than the suggested cut level of 10%, with all classes exceeding average posterior probabilities of 0.75. The assumption of local independence was also accepted after assessing bivariate residuals. Although overall entropy was slightly less than the suggest entropy of greater than .70, clinical justification and interpretability out- weighted some of these limitations, see Tables 2 and 3.

We considered chronic illnesses that occurred in more than 50% of the class as significant chronic illnesses for each class. Class I, labeled as the depression class, comprised 17.7% of the sample (n=228) and chronic illnesses consisted of hypercholesterolemia, depression and arthritis. Class II, labeled as the sleep class, comprised 10.6% of the sample (n=136) and

chronic illnesses present in this group were hypercholesterolemia, sleep disturbances, and sleep apnea. Class III, labeled as the cardiovascular class, comprised 21% of the sample (n=270) and chronic illnesses in this group were hypercholesterolemia, hypertension and arthritis. Class IV, labeled as the healthy class, was the largest class and comprised 50.7% of the sample (n=651); no chronic illnesses were present in greater than 25% of the sample.

3.3 Validation of the four-class solution

We further validated the classes by using BCH to compare various biometric health indicators and depression scores. Indeed, in our analysis, there were differences between class II (sleep class) and the other three classes and between class IV (healthy class) and the other three classes in the distribution of participant BMI and hs- CRP levels. Differences between each class and at least two other classes were noted on the distribution of participant Interleukin-6 (IL-6) and glucose levels, as well as Center for Epidemiological Studies Depression scale (CES-D) scores. See Table 4.

3.4 Four class solution and relationship to cognition

To test whether MCC in general was related to the presence of aMCI or naMCI, the four-class solution was dichotomized into two groups - MCC (Classes 1–111) and non-MCC (Class IV). Chi-square statistic revealed no significant difference in the proportion of participants with aMCI and MCC ($\chi^2 = 0.27$, $p = 0.61$) and the proportion of participants with naMCI and MCC ($\chi^2 = 0.04$, $p = 0.83$).

Chi-square statistic revealed a significant difference in the proportion of participants with aMCI between the classes ($\chi^2 = 8.46$, $p = 0.03$), with the largest differences observed between classes II (19%) and III (9%) ($p < 0.01$) and classes II (19%) and IV (12%) ($p < 0.01$). The incidence of naMCI was lower than aMCI and the proportion of naMCI did not differ across classes. See Table 5.

4. Discussion

It is widely recognized that individual chronic illnesses are associated with cognitive decline; however, the literature exploring the relationship between MCC and cognition is limited. Logic would dictate that if one chronic illness is a risk for cognitive decline, the presence of MCC may have multifaceted effects on cognition. Given the high prevalence of MCC in older adults, we proposed to examine the relationship between MCC and cognition in a cohort of late middle-aged adults. We found four distinct classes of chronic illness in the WRAP cohort: a depression class (cholesterol, depression, and arthritis), a sleep class (cholesterol, sleep disturbances, sleep apnea), a cardiovascular class (cholesterol, hypertension, arthritis) and a healthy class (all chronic illnesses occurred at less than 25%). Several findings support this four-class solution. First, general MCC was not related to aMCI or naMCI. However, the proportion of new-onset aMCI differed between MCC classes offering initial evidence of an association between specific MCC clusters and the development of aMCI. Differences in key biometric health indicators between the classes provides additional strength to this four-class solution.

Latent class analysis represents a novel method for identifying MCC clusters. This methodology allows for more comprehensive view of individuals at risk for cognitive decline and subsequent AD. Further, results provided are much more generalizable to a population of older adults where MCC is the norm rather than the exception.

Our finding that the proportion of new-onset aMCI differed between MCC classes offers initial evidence of an association between MCC and the development of aMCI. Surprisingly, participants in class II (sleep) had the highest incidence of new onset aMCI, even higher than those in class III (cardiovascular). Further, our finding that naMCI was not associated with MCC in our sample suggests that the relationship between MCC and cognitive decline may be specific to the memory domain. While no other studies have explored the effects of MCC on cognitive decline among non-demented individuals, our findings are consistent with evidence of an association between MCC and accelerated cognitive decline among individuals with dementia. Melis *et al.*, followed 310 persons with incident dementia over approximately 5 years and reported that those with MCC experienced accelerated cognitive decline compared to those without MCC [27]. Further, Aubert *et al.*, found that MCC was associated with a 30% greater rate of decline among older adults with AD [28]. However, neither of these investigators differentiated between naMCI and aMCI since both samples were already demented prior in the analysis.

Pending further evidence, our findings suggest that specific MCC clusters (classes) increase cognitive aging, specifically in the memory domain and may represent a potentially modifiable risk factor for AD. Nurse led chronic illness prevention programs and improved self-management of existing chronic illnesses may decrease the risk of cognitive decline and AD. As our cohort ages, we will follow not only the incidence and rate of cognitive decline between the classes, but also the incidence of AD and dementia in order to provide a more comprehensive depiction of the effects of MCC on risk of AD.

Two findings from this study were of particular interest, the low incidence of cognitive impairment in class III (cardiovascular) and the presence of hypercholesterolemia across all classes. Recent literature has suggested a positive relationship between cholesterol, other cardiovascular conditions and cognitive decline and subsequent AD [29]. However, our findings would suggest that sleep is a stronger risk for accelerated cognitive aging than cardiovascular conditions. Previous literature documents that sleep is essential for memory consolidation and brain functioning [30, 31], Disruptions in sleep may interfere with the neural pathways and might damage brain plasticity [32, 33], Sleep disturbance and sleep apnea are common in people with AD and these factors are found to be correlated with AD biomarkers, such as phosphorylated tau and amyloid plaques[34–36]. Sleep fragmentation and hypoxia from sleep apnea are the two mechanisms known to be associated with altering cognition [37], In animal studies, hypoxia could lead to oxidative stress and inflammation in the brain, and thereby increase the cell deaths and decrease the hippocampal volume [38], This study adds to current literature on how sleep is associated with MCI in the context of MCC. More studies are needed to investigate the more in-depth underlying etiology of connection across sleep and cognition and AD pathology.

Hypercholesterolemia was present in every class in our sample. This finding is not unusual for AD cohorts and the WRAP cohort is comprised primarily of adults at risk for AD by virtue of family history. The prevalence of hypercholesterolemia in the WRAP (63%) is much higher than the general US population (32%). When hypercholesterolemia was removed from the model, the classes disintegrated; suggesting that hypercholesterolemia is an important chronic illness in the MCC model. Hypercholesterolemia may serve as the pivotal disease - *i.e.*, the disease that sets into motion cognitive changes in the presence of other illnesses. As documented in several reviews, previous findings regarding the role of cholesterol in the development of dementia have been controversial [29, 39, 40]. As stated by Wanamaker *et al.*, the role of cholesterol and the development of AD is likely complex because the brain fabricates most of its own cholesterol and cholesterol does not easily cross the blood-brain barrier [29]. Koch and Jensen, in a recent review recommend that future studies investigate the effect of cholesterol in the context of MCC [39]. Our findings support the hypothesis that the relationship between cholesterol and cognitive decline is complex, but that cholesterol likely plays a role in the accelerated cognitive aging that leads to dementia. Future studies are needed to confirm our findings and further elucidate the cholesterol's role in dementia development.

4.1 Limitations

Our findings should be taken in the context of key limitations. Our design does not allow for an investigation of the temporal relationship between MCC and cognitive decline. As a study by Melis et al., 2014 suggests, cognitive decline may be a predictor of MCC. After following over 400 participants for over 3 years the authors concluded that worse cognitive function was associated with an increased risk of MCC (OR 1.22, 95% CI 1.00–1.48) [27]. *A priori* designs with attention to MCC are needed. Our cohort is still relatively young and the phenotypes of clinical cognitive impairment and dementia are still evolving. Future prospective studies should focus on older cohorts in order to increase the number of participants who are diagnosed with cognitive impairment and dementia. As our team continues to follow our cohort and as the incidence of clinical cognitive impairment and AD increases, we will be able to revisit and re-test the model with a goal of documenting a model that identifies early life risk factors for AD. Chronic illnesses were assessed via self-report, a common practice in many large cohort studies such as WRAP. Self-report may lead to under/over-reporting of conditions; however, the WRAP cohort is well educated and cognitively intact at enrollment. Participants were asked at 3 different visits to report or verify chronic illnesses to minimize errors.

4.2 Conclusions

This is the first study to explore the relationship between MCC and mild cognitive impairment. Our study has important implications for nursing clinical practice and future research studies. The four-class solution provides a new line of thinking about AD risk and insights into MCC self-management prioritization (*e.g.*, sleep disorders may be more detrimental to brain function than HTN). Nursing interventions aimed at improved prevention and self-management of chronic illnesses may improve outcomes by decreasing AD incidence/progression. Future studies are needed to confirm our findings. Finally,

neuroimaging studies could augment current findings by documenting volumetric, structural and micro/macro-perfusion changes that may be present early in the MCC trajectory and signify downstream cognitive changes.

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Highlights

- Multi-morbidity represents a paradigm shift in the study of Alzheimer's disease
- Certain chronic illness clusters may signify increased risk for Alzheimer's disease
- Improved chronic illness management may support in Alzheimer's disease prevention

Figure 1. Four-class solution

x-axis= chronic illness; y-axis=percent of participants per class reporting specific chronic illness

Table 1:

Sample Characteristics

	Total Sample (n=1285)		I: Depression (n = 228)	II: Sleep (n=136)	III: Cardiovascular (n=270)	IV: Healthy (n=651)
Age (range = 36–68)	53.69 (6.52)	53.58 (6.21)	55.39 (5.86) ^a	55.83 (6.24) ^{ab}	52.48 (6.58)	
Gender: Female *	901 (70.1)	193 (84.6) ^{cd}	79 (58.1)	198 (73.3) ^{ef}	431 (66.2)	
Race(n=1284)						
• White/Caucasian	1214(94.5)	214(93.9)	124 (91.2)	253 (93.7)	623 (95.8)	
• Black/AA	48 (3.7)	11 (4.8)	8 (5.9)	12 (4.4)	17 (2.6)	
• Spanish/Hispanic	11 (.9)	0	1 (.7)	3 (1.1)	7(1.1)	
• American Indian	9 (.7)	3 (1.3)	3 (2.2)	1 (.4)	2 (.3)	
• Asian	2 (.2)	0	0	1 (.4)	1 (.2)	
Marital (n=1283)						
• Married	965 (75.2)	160 (70.5)	102 (75.0)	200 (74.1)	503 (77.4)	
• Divorced	155 (12.1)	32 (14.1)	17 (12.5)	31 (11.5)	75 (11.5)	
• Separated	8 (.6)	2 (.9)	0	4(1.5)	2 (.3)	
• Widowed	32 (2.5)	9 (4.0)	2(1.5)	8 (3.0)	13 (2.0)	
• Never married	99 (7.7)	18 (7.9)	12 (8.8)	21 (7.8)	48 (7.4)	
• Living with partner	24 (1.9)	6 (2.6)	3 (2.2)	6 (2.2)	9 (1.4)	
Education						
• Some HS	1 (.1)	0	0	0	1 (.2)	
• HS graduate or GED	112 (8.7)	24 (10.5)	6 (4.4)	23 (8.5)	59 (9.1)	
• Some college or tech school	388 (30.2)	61 (26.8)	52 (38.2)	88 (32.6)	187 (28.7)	
• College graduate	384 (29.9)	78 (34.2)	38 (27.9)	71 (26.3)	197 (30.3)	
• Post-graduate	400 (31.1)	65(28.5)	40 (29.4)	88 (32.6)	207 (31.8)	
Education in yrs (range=11–28)	16.15(2.76)	16.18(3.02)	16.10 (2.39)	16.05 (2.72)	16.20 (2.77)	
Employment Status						

	I: Depression (n = 228)	II: Sleep (n=136)	III: Cardiovascular (n=270)	IV: Healthy (n=651)
Total Sample (n=1285)				
• Full-time	132 (57.9)	81 (59.6)	147 (54.4)	419 (64.4)
• Part-time	49 (21.5)	21 (15.4)	50 (18.5)	127 (19.5)
• Unemployed	24 (10.5)	21 (15.4)	37 (13.7)	74 (11.4)
• Retired	23 (10.1)	13 (9.6)	36 (13.3)	31 (4.8)
Family Hx of Alzheimer's disease	173 (75.9)	94 (69.1)	199 (73.7)	476 (73.1)

Values given as Mean (SD) or N (%)

AA = African American; HS = high school

*
 $p < .001$

^a compared to Class IV ($p < .001$)

^b compared to Class I ($p < .01$)

^c compared to Classes II & IV ($p < .001$)

^d compared to Class III ($p < .01$)

^e compared to Class II ($p < .01$)

^f compared to Class IV ($p < .05$)

Table 2.

Model Fit

Classes	AIC	BIC	aBIC	Entropy
1	15822.873	15895.092	15850.621	-
2	15337.084	15486.681	15394.563	0.663
3	15163.565	15390.540	15250.774	0.686
4*	15058.561	15362.913	15175.499	0.669
5	15040.015	15421.745	15186.684	0.678

Table 3.

Model Fit

Class comparison	VLMR LRT	LRM LRT
1 versus 2	<0.001	<0.001
2 versus 3	0.02	0.02
3 versus 4	0.002	0.002
4 versus 5	0.344	0.348

Table 4.

Validation of four-class solution

	Total Sample	I: Depression	II: Sleep	III: Cardiovascular	IV: Healthy
BMI [*] (n=909)	29.16 (6.48)	29.84 (7.16) ^a	34.12 (7.73) ^{abc}	30.36 (6.62) ^a	27.50 (5.18)
hs-CRP [*] (n=1254)	2.67 (3.80)	2.78 (3.30) ^d	4.51 (5.49) ^{ace}	2.84 (3.68) ^d	2.19 (3.45)
IL6 ^{**} (n=1197)	2.11 (3.35)	2.06 (1.72)	2.53 (1.80) ^{af}	2.60 (4.87) ^d	1.83 (3.22)
Glucose [*] (n=1260)	98.07 (20.49)	96.65 (25.65)	105.32 (27.15) ^{ae}	104.90 (26.75) ^{ab}	94.20 (10.17)
CESD [*] (n=1121)	7.40 (6.84)	10.85 (8.75) ^{ag}	9.79 (8.50) ^{ag}	5.76 (5.16)	6.21 (5.48)

Values given as Mean (SD)

BMI = body mass index; IL6 = interleukin 6; hs-CRP = high-sensitivity C-reactive protein; CESD = Center for Epidemiological Studies Depression Scale

^{*}
 $p < .001$ ^{**}
 $p < .01$ ^a
compared to Class IV ($p < .001$)^b
compared to Class I ($p < .001$)^c
compared to Class III ($p < .01$)^d
compared to Class IV ($p < .05$)^e
compared to Class I ($p < .01$)^f
compared to Class I ($p < .05$)^g
compared to Class III ($p < .001$)

Table 5.

Mild cognitive impairment by class

	Total Sample	I: Depression	II: Sleep	III: Cardiovascular	IV: Healthy
	(n=1285)	(n = 228)	(n=136)	(n=270)	(n=651)
aMCI [*]	158 (12.3)	30 (13.16)	26 (19.12) ^a	25 (9.26)	77 (11.83)
naMCI	85 (6.61)	20 (8.77)	8 (5.88)	13 (4.81)	44 (3.76)

Values given as N (%)

aMCI= amnesic mild cognitive impairment; naMCI=non-amnesic mild cognitive impairment

^{*}
 $p<.05$ ^a
compared to Class III ($p<.01$) and Class IV ($p<.01$)