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Original article

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 1285 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.

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 interventions.

1. Background

Alzheimer's disease is the 6th leading cause of death and the only leading cause of death whose prevalence continues to grow (Anderson, 2010). 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 (Arvanitakis et al., 2006; Biegler, Chaoul, & Cohen, 2009; Bratzke-Bauer et al., 2013; Iadecola et al., 2016; Shin et al., 2012), but researchers have largely ignored the effects of multi-morbidity on cognition and risk of ADRD. Multiple chronic conditions (MCC) are the presence of two or more chronic conditions 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 (Anderson, 2010). 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 (Aarts et al., 2011; Boyd & Fortin, 2010; Bratzke et al., 2015; Griffith et al., 2010; Koroukian et al., 2015). 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

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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 condition 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 (Jonaitis et al., 2013; Sager, Hermann, & La Rue, 2005). 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 (Mckhann et al., 1984). 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' post-baseline (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 1285. 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 (Radloff, 1977).

2.3.2. Neuropsychological tests

A battery of commonly used cognitive tests was administered at baseline and at each subsequent visit. See Sager et al., 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 (Koscik et al., 2014), 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 amnestic mild cognitive impairment (aMCI) if memory factor scores were below threshold or psychometric non-amnestic 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 & Muthen, 2017) 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 $>$ 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 (Fraley & Raftery, 1998; Lo, Mendell, & Rubin, 2001; Nylund, Asparouhov, & Muthen, 2007).

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 (Asparouhov & Muthen, 2014; Bolck, Croon, & Hagenaars, 2004; Vermunt, 2010). 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 (Fig. 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 $>$ 0.70, clinical justification and interpretability outweighted some of these limitations, see Tables 2 and 3.

We considered chronic illnesses that occurred in $>$ 50% of the class as significant chronic illnesses for each class. Class I, labeled as the