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Identifying Patterns of Multimorbidity in Older Americans: Application of Latent Class Analysis

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ABSTRACT

Objectives: To empirically define multimorbidity "classes" based on patterns of disease co-occurrence among older Americans and to examine how class membership predicts healthcare utilization.

Design: Retrospective cohort study

Setting: Nationally representative sample of Medicare beneficiaries in file years 1999-2007

Participants: 14,052 participants age ≥65 years in the Medicare Beneficiary Survey who had data available for at least 1 year after index interview

Measurement: Surveys (self-report) assessed chronic conditions; latent class analysis (LCA) was used to define multimorbidity classes based on the presence/absence of 13 conditions. All participants were assigned to a best-fit class. Primary outcomes were hospitalizations and emergency department visits over one year.

Results: Our primary LCA identified six classes. The largest portion of participants (32.7%) was assigned to the 'Minimal Disease' Class, in which most persons had ≤ 1 of the conditions. The other five classes represented various degrees and patterns of multimorbidity. Utilization rates were higher in classes with greater morbidity, compared to the Minimal Disease Class. However, many individuals could not be assigned to a particular class with confidence (sample misclassification error estimate = 0.36). Number of conditions predicted the outcomes at least as well as class membership.

Conclusion: Although recognition of general patterns of disease co-occurrence is useful for policy planning, the heterogeneity of persons with significant multimorbidity (≥3 conditions) defies neat classification. A simple count of conditions may be preferable for predicting utilization.

Key words: health service use; complexity; comorbidity

INTRODUCTION

One in four American adults has multimorbidity, defined as the co-occurrence of at least two chronic conditions[1,2]. Because the prevalence of many conditions increases with age, multimorbidity is increasingly common throughout the lifespan[1]. Approximately one-third of Medicare beneficiaries over age 65 have four or more conditions[1]. Due to demographic trends, the prevalence and severity of multimorbidity is expected to continue rising over the next decades[3,4].

Although the majority of older patients exhibit multimorbidity, most treatment plans and clinical guidelines target single diseases[5]. When the "single-disease paradigm" is rigidly applied to people with significant multimorbidity, the resultant care plans may be impractical or even harmful[5,6]. An intervention that is good for one disease may be less effective, irrelevant, or deleterious in the presence of co-existing conditions[6,7].

Similarly, well-intended policies, such as disease-based quality metrics, can inadvertently incentivize burdensome and inappropriate care plans for patients with multimorbidity[5].Due in part to these challenges, multimorbidity is associated with high rates of death, disability, complications, poor quality of life, and healthcare utilization[8,9]. Thus, it is important for quality surveillance programs and clinical research initiatives to accurately account for multimorbidity[10].

At present, there exists little guidance about best practices for treating multimorbid individuals and tracking their health outcomes. It is impractical to devise individualized algorithms for all potential disease combinations, but common approaches such as counting the number of conditions or the number of affected organ systems may be overly simplistic[11,12].

The analyses presented here are based on the hypothesis that many common conditions cluster together in the population in predictable patterns. For example, certain disease clusters may be driven by common genetic propensity, lifestyle, or environmental exposures. We hypothesized that: 1) patients can be classified based on which multimorbidity pattern most closely matches their array of comorbidities, and 2) class membership predicts healthcare utilization. Our objective was to empirically define multimorbidity "classes",based on the pattern of co-occurrence of 13 common chronic conditions. We applied latent class analysis (LCA), a type of structural equation modeling used to identify sub-groups based on a set of observed variables[13]. The identification and validation of major classes of multimorbidity might help organize specific treatment strategies, research agendas, and system-wide initiatives aimed at improving care for people with various types and degrees of multimorbidity.

METHODS

Data Source

This study is a secondary analysis of data from the Medicare Current Beneficiary Survey (MCBS) Cost and Use files (1999–2007) and linked Medicare claims. The MCBS is a continuous survey of a nationally representative sample of Medicare beneficiaries. The MCBS sample is stratified according to age (with oversampling of persons aged ≥85) and drawn within ZIP code clusters.. Participants are interviewed in person three times per year. If the participant is unable to answer questions, a proxy respondent is designated. Results from the self-report survey are combined with Medicare claims data. Approval for the study was obtained from the institutional review board of Duke University Medical Center.

Sample

MCBS participants who were community-dwelling at their index interview (file years 1999-2006), eligible for Medicare on the basis of age (≥ 65 years), and enrolled in Medicare Fee-for-Service were eligible MCBS operates on a 4-year rotating panel design; subjects enter and leave the survey each year. Participants in this analysis contributed data for at least one year after their index interview to ascertain 12-month utilization outcomes. After applying these criteria, the final analytical sample size was 14,052 individuals.

Measures

Self-reported demographic variables included age, sex, race (white or non-white), highest education level (< high school, high school degree, ≥ college), and marital status. Presence or absence of 13 health conditions were obtained by self-report ("Have you ever been told that you have…?"): hypertension (HTN), arthritis (rheumatoid and/or non-rheumatoid), osteoporosis, diabetes mellitus (DM), non-skin cancer, mental or psychiatric disorder, emphysema or chronic obstructive pulmonary disease (COPD), stroke, Alzheimer's disease (AD), Parkinson's disease

(PD), heart arrhythmia, congestive heart failure (CHF), and coronary heart disease (CHD), which included myocardial infarction/heart attack, angina pectoris, or CHD.

Dates and types of health service use were identified in CMS standard analytical files. Outcomes of interest were dichotomous measures of any inpatient admission or any emergency department (ED) visit within 12 months.

Analysis

Primary Analysis

In LCA models, variation of observed indicators (e.g., presence or absence of 13 chronic health conditions) is modeled as a function of membership in unobserved (latent) classes. Class membership is probabilistic, with probabilities computed from the estimated model parameters.

First, increasingly complex models (adding more latent classes) were estimated to determine the optimal number of latent classes to fit the data. The Bayesian Information Criterion (BIC) reflects the likelihood function (i.e., how well the model predicts the data) and the number of parameters in the model. Models with smaller BICs are preferable. We compared candidate models' BICs and applied substantive interpretability and clinical judgment (i.e., Do the classes defined by a given model possess a clinical significance or meaning?).

After selecting a latent class model, we assigned each participant to his or her "best fit" class, meaning the class for which the participant had the highest computed probability of membership.

Finally, regression models were used to examine the relationship between class membership and the dependent variables (hospitalization, ED visit). LCA was performed using the Latent Gold software package (Statistical Innovations, Belmont, MA), which quantifies model entropy and misclassification error. Other analyses were conducted using SAS version 9.3 (SAS Institute, Inc., Cary, NC).

Secondary Analyses

After reviewing primary analysis results, we pursued secondary, exploratory analyses for two purposes. The first purpose was to determine whether, by altering the observed variable set used to "train" the LCA model, we could derive a superior set of latent multimorbidity classes that provided better data fit and improved entropy, while retaining disease clusters that were clinically meaningful.

The second purpose was to compare the predictive ability of latent class membership to the predictive ability of a simple count of chronic conditions. In regression models in which our utilization outcomes were the dependent variables, we compared models where the primary independent variable was either latent class membership or a simple morbidity count, as well as models that included both independent variables.

RESULTS

Determining the Optimal Number of Latent Classes

The smallest (i.e., most optimal) BIC values were obtained for the 5-class (BIC 151950) and 6-class (BIC 151937) candidate models. Because the difference in BIC values between the 5-class and 6-class models was so small, we considered the merits of both models. We selected the 6-class model for the next steps in our primary analysis (See on-line appendix).

The six classes were labeled based on which conditions exhibited excess prevalence (i.e., prevalence in class exceeds prevalence in full cohort): Minimal Disease Class (prevalence of all conditions is below cohort average), Non-Vascular Class (excess prevalence in cancer, osteoporosis, arthritis, arrhythmia, COPD, and psychiatric disorders), Vascular Class (excess prevalence in HTN, DM, and stroke), Cardio-Stroke-Cancer Class (excess prevalence in CHF, CHD, arrhythmia, stroke and to a lesser extent HTN, DM, cancer), Major Neurologic Disease Class (excess prevalence in AD, Parkinson's disease, psychiatric disorders), and Very Sick Class (above-average prevalence of all 13 conditions).

Characteristics of Class Members

Every participant was assigned to one of the six classes based on highest calculated probability of membership. Demographics and health status for each class are displayed in Table 1. The Minimal Disease Class comprised the largest group (32.7% of cohort), in which most members had 0 or 1 condition and tended to be younger and more educated. Other classes exhibited varying degrees of multimorbidity, ranging from a mean of 2.8 conditions in the Non-Vascular Class to 6.3 conditions in the Very Sick Class. Age ranges were similar across classes (75.5 to 77.6 years), with the exception of the Major Neurologic Disease Class (mean age 80.7 ± 7.7 years), in which almost 9 in 10 members reported AD. The proportion of males was highest in the Cardio-Stroke-Cancer Class, whereas the proportion of females was highest in the Non-

Vascular Class. The Very Sick Class was demographically similar to the Major Neurologic Disease Class, although Very Sick Class members were typically younger (77.0 ± 7.6 years).

Relationship Between Multimorbidity Class Membership and Outcomes

The odds of hospital admission and ED use over a 1-year period, by multimorbidity class, are displayed in Figure 1. The Minimal Disease Class is used as the reference group, because its members had the lowest odds of utilization. Among participants assigned to the Minimal Disease class, the 1-year rate of ED use was 10.9% and the 1-year rate of hospitalization was 8.9%. In analyses that adjusted for age, sex, race, and education, the odds of utilization were higher in classes with higher disease burden. The highest odds of utilization occurred in the Very Sick Class: the adjusted odds ratio for ED use was 3.2 (95% confidence interval [CI] = 2.7 to 3.7) and the adjusted odds ratio for hospitalization was 5.2 (95% CI = 4.4 to 6.1).

Model fit and misclassification error

Misclassification error was estimated at 0.36 for the sample. In other words, approximately 1 in 3 participants exhibited a pattern of multimorbidity that was a poor fit for any class or was similarly probable in multiple classes. Of the 14052 participants, only 5628 (40.1%) had ≥0.70 calculated probability of membership in the "best-fit" class to which they were assigned; 11781 (83.4%) had ≥0.40 probability. Mean membership probabilities for individuals assigned to the six classes ranged from 0.48 (Cardio-Stroke-Cancer Class) to 0.75 (Minimal Disease Class).

Attempts to Estimate a Better-fit Model

In an effort to reduce misclassification error, we first added "number of chronic conditions" as a 14th observed variable. This strategy produced models with negligible misclassification error (estimate < 0.01), but the latent classes were defined almost entirely by comorbidity count, rather than patterns of disease co-occurrence. Judging by BIC values alone, the 2-class model was optimal and it sorted participants into a low disease prevalence class (0-2 conditions) or a high disease prevalence class (3-11 conditions), with no overlap.

Next, we estimated LCA models using fewer indicator variables. We first eliminated hypertension, osteoporosis, and psychiatric disorders because 1) hypertension and osteoporosis were not strong independent predictors of the outcomes and 2) by eliminating psychiatric disorders, the analysis focused on medical comorbidities. We then eliminated arthritis, cancer, and diabetes, based on relatively weak independent relationship with utilization outcomes. In LCA models based on 7 or 10 indicator variables, misclassification error remained high.

Comparison of Multimorbidity Class vs. Simple Disease Count as Predictors of Outcomes

Table 2 summarizes the predictive power of multiple adjusted logistic regression models predicting 1-year hospitalization or ED use. A comparison of the c-statistic calculated for each model suggests that the models explain similar variance in the utilization outcomes regardless of whether the multimorbidity indicator(s) were multimorbidity class membership (Model 1), a simple count of diseases (Model 2), or both indicators (Model 3). For the outcome of ED utilization, morbidity count remained a significant independent predictor ($p<0.001$) in Model 3, whereas the significance of class membership as an independent predictor was degraded ($p = 0.052$).

DISCUSSION

To our knowledge, this is the first study to empirically characterize broad patterns of multimorbidity clusters within the Medicare population. Many tools and indices are available to quantify multimorbidity burden[12,14], but this study aimed to define categories of multimorbidity in qualitative terms, based on natural patterns of clustering in the population. The LCA identified six statistically distinct and clinically meaningful classes of multimorbidity, based on the presence or absence of 13 common conditions. However, a key insight is that the application of these empirically-derived classes to individual patients is challenging. The models exhibited high misclassification error, indicating that many participants with multimorbidity could not be confidently assigned to a group. While the recognition of major patterns of disease co-occurrence may help organize prevention and treatment initiatives, a simple count of conditions was an equally informative means of risk-stratifying the population. Considering that many beneficiaries did not fit neatly into a particular group, treatment plans for people with significant multimorbidity demand an individualized approach.

Prior studies have applied LCA, in different populations, to identify patterns of co-occurring conditions. Pugh et al. identified latent classes based on co-occurrence among 32 medical, psychiatric, and deployment-specific conditions in 191,797 Veterans[15]. Compared to the Medicare beneficiaries, the younger Veteran population exhibited a significantly different spectrum of disease, including prevalent PTSD, pain, traumatic brain injury, and substance abuse. Pugh's analysis also derived a model with 6 classes, the largest of which exhibited minimal disease burden (53% of cohort)[15]. In a second study, Islam et al. employed several analytical approaches, including cluster analysis, principal components analysis, and LCA, to describe patterns or clusters of 10 conditions among 4574 older Australians[16]. The Islam et al. LCA yielded a 4-class model, and the largest group was again a group with minimal disease (55.5% of cohort). The other three groups in Islam's study resembled our Non-vascular Class (high arthritis, asthma, depression), Vascular Class (high diabetes, hypertension) and Cardio-Stroke-Cancer group (high heart disease, stroke, cancer)[16]. Neither the Pugh nor the Islam study reported model entropy or misclassification error estimates.

High misclassification error diminishes enthusiasm for the clinical applicability of LCA-derived multimorbidity classes in guiding individual care decisions. Nonetheless, the similarities between the classes that emerged here and in the Islam study[16] supports the existence of broad disease clustering patterns in older adults. The patterns reflect plausible disease clusters which share similar underlying etiologies or risk factors. For example, the Vascular group is characterized by diabetes and hypertension, which are part of the metabolic syndrome and are known risk factors for vascular disease[17]. The older Cardio-Stroke-Cancer group may implicate shared risk factors for cancer and vasculopathy (e.g., smoking).

In a previous study, Kao et al. constructed LCA models based on 27 clinical features to identify phenotypes of people with heart failure[18]. The Kao analysis identified clinically plausible subtypes of heart failure and class membership was predictive of treatment response. The authors did not discuss misclassification error in class assignment[18]. Future work should examine whether considering clinical traits aside from comorbidity might improve identification of important phenotypes in persons aging with multimorbidity.

Our study has several limitations. Chronic conditions were identified based on self-report, which may not reflect true disease occurrence and lacks information on disease severity and chronicity. The relationships described may be confounded by factors not controlled for here. Our analysis excluded long-term care residents and does not address health outcomes other than utilization.

Nonetheless, this study is a novel application of LCA to identify patterns of multimorbidity within a representative sample of Medicare beneficiaries. Six classes of disease co-occurrence emerged, and these multimorbidity patterns were clinically recognizable and theoretically plausible. Application to decision-making on individual patients is limited by the fact that many persons with multimorbidity do not fit neatly into one of the six classes. This caveat to the use of LCA-derived groups has not been addressed in prior studies on this topic. Future research that applies LCA to identify sub-groups or phenotypes among older patient populations should consider and report model entropy and misclassification error.

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Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

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Acquisition of subjects and/or data: Susan N. Hastings

Analysis and interpretation of data: all authors

Preparation of manuscript: all authors

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TABLE 1: Characteristics of Persons Assigned to Six Multimorbidity Classes

Characteristic	Total Sample (N=14,052)	Minimal Disease (N=4613) 32.8%	Non-Vascular (N=3509) 25.0%	Vascular (N=3211) 22.9%	Cardio-Stroke-Cancer (N=1165) 8.3%	Neuro. Disease (N=396) 2.8%	Very Sick (N=1158) 8.2%
Age, M ± SD[a]	76.4±7.3	75.5±7.1	77.0±7.3	76.0±7.1	77.6±7.4	80.7±7.7	77.0±7.6
Sex, % Male	43.5%	52.7%	23.8%	46.3%	64.4%	39.1%	38.5%
Race, % White	86.8%	88.1%	90.3%	81.0%	89.9%	81.1%	86.1%
Highest Education Level							
Less than High School	29.7%	25.7%	27.7%	32.1%	31.2%	42.4%	39.2%
High School Degree	50.5%	50.9%	53.1%	49.6%	48.8%	43.2%	47.8%
College or Beyond	19.8%	23.4%	19.2%	18.3%	19.9%	14.4%	13.0%
Marital Status, % Married	53.9%	61.0%	47.9%	53.0%	59.8%	45.2%	44.0%
Number of 13 Diagnoses, M ± SD	2.8±1.8	1.1±0.8	3.5±1.0	2.8±0.9	3.8±0.9	4.7±1.5	6.3±1.1
Prevalence of Condition							
Parkinson's Disease	1.3%	0.9%	0.9%	0.9%	0.6%	12.9%	2.6%

Alzheimer’s Disease	3.5%	1.1%	0	0.1%	2.4%	87.9%	5.4%
Psychiatric Disorders	14.2%	2.4%	24.0%	9.1%	2.3%	54.8%	43.8%
Stroke	11.7%	2.5%	6.5%	15.7%	20.8%	38.4%	35.0%
Arthritis	61.6%	26.0%	94.1%	71.9%	41.2%	71.7%	93.7%
Cancer	18.6%	14.7%	28.5%	10.3%	21.7%	15.7%	24.7%
Osteoporosis	20.6%	7.1%	56.8%	1.6%	1.8%	29.8%	32.7%
COPD[b]	14.8%	8.0%	23.5%	3.1%	14.3%	12.9%	49.4%
Hypertension	63.9%	27.8%	47.1%	100%	71.4%	67.2%	90.6%
Diabetes	20.7%	6.0%	28.8%	41.7%	27.7%	20.2%	49.7%
Arrhythmia	20.8%	6.3%	44.0%	4.3%	65.4%	16.9%	64.1%
CHD[c]	25.3%	5.4%	15.0%	25.6%	74.0%	33.8%	83.3%
CHF[d]	7.3%	0	1.0%	0%	31.5%	3.3%	52.9%

[a]SD = standard deviation

[b]COPD = chronic obstructive pulmonary disease

[c]CHD = coronary heart disease

[d]CHF = congestive heart failure

TABLE 2: Comparing Regression Models with Different Multimorbidity Indicators as Predictors of Acute Care Utilization

Model[b]	ED[a] Visit in 1 Year				Hospital Admission in 1-year			
	DF[c]	Wald χ^2	p value	C-statistic[d]	DF	Wald χ^2	p value	C-statistic
Model 1 Multimorbidity Class	5	260.5	<0.001	0.627	5	470.0	<0.001	0.667
Model 2 Morbidity Count	1	325.1	<0.001	0.639[e]	1	533.3	<0.001	0.678[e]
Model 3 Multimorbidity				0.640[e]				0.682[e]

Class	5	10.9	0.05	5	32.4	<0.001
Morbidity Count	1	74.9	<0.001	1	94.4	<0.001

[a]ED = emergency department

[b]All models are adjusted for age, race, sex, and education level

[c]DF = degrees of freedom

[d]The c-statistics for Models 2 and 3 were unchanged, regardless of whether "morbidity count" was treated as a continuous vs. class variable. Parameters presented here are taken from analyses that treated morbidity count as a continuous variable (possible range 0-13); multimorbidity class was treated as a nominal class variable with 6 levels.

[e]C-statistic is significantly different (p<0.001) from the c-statistic for Model 1, as assessed by the DeLong test[19]. C-statistics of Models 2 and 3 were not significantly different from each other (p=0.861 for outcome of ED visits; p=0.170 for outcome of hospital admission).

FIGURE 1: Odds of Acute Care Utilization, According to Multimorbidity Class

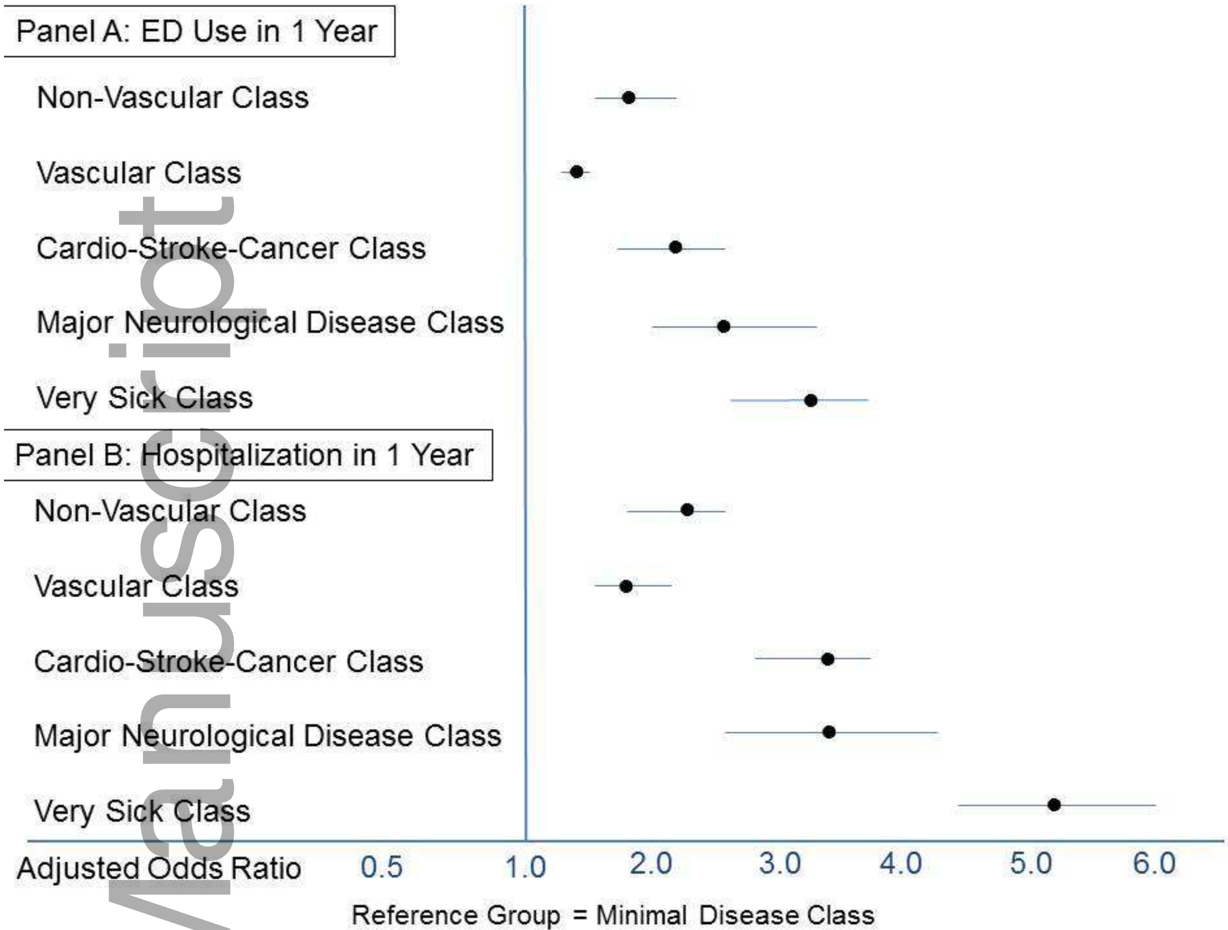

FIGURE LEGEND: In logistic regression models that were adjusted for age, race, sex and education level, membership in any one of the "multimorbidity classes" was associated with higher odds of Emergency department (ED) use and hospitalization over 1 year, compared to membership in the Minimal Disease class.