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

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

DESIGN: Retrospective cohort study.

SETTING: Nationally representative sample of Medicare beneficiaries in file years 1999–2007.

PARTICIPANTS: Individuals aged 65 and older in the Medicare Beneficiary Survey who had data available for at least 1 year after index interview (N = 14,052).

MEASUREMENTS: Surveys (self-report) were used to assess chronic conditions, and latent class analysis (LCA) was used to define multimorbidity classes based on the presence or absence of 13 conditions. All participants were assigned to a best-fit class. Primary outcomes were hospitalizations and emergency department visits over 1 year.

RESULTS: The primary LCA identified six classes. The largest portion of participants (32.7%) was assigned to the minimal disease class, in which most persons had fewer than two of the conditions. The other five classes represented various degrees and patterns of multimorbidity. Usage rates were higher in classes with greater morbidity, but many individuals could not be assigned to a particular class with confidence (sample misclassification error estimate = 0.36). Number of conditions predicted 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 usage. **J Am Geriatr Soc 64:1668–1673, 2016.**

Key words: health service use; complexity; comorbidity

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 over the lifespan.[1] Approximately one-third of Medicare beneficiaries aged 65 and older have four or more conditions.[1] Because of demographic trends, the prevalence and severity of multimorbidity is expected to continue rising over the next decades.[3,4]

Although the majority of older adults have 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 coexisting conditions.[6,7]

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

There is little guidance about best practices for treating individuals with multimorbidity 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

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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, common genetic propensity, lifestyle, or environmental exposures may lead to certain disease clusters. It was hypothesized that individuals can be classified based on which multimorbidity pattern most closely matches their array of comorbidities and that class membership predicts healthcare use. The objective was to define multimorbidity "classes" empirically based on the pattern of co-occurrence of 13 common chronic conditions. Latent class analysis (LCA), a type of structural equation modeling used to identify subgroups based on a set of observed variables, was applied.[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 of people with various types and degrees of multimorbidity.

METHODS

Data Source

This study was 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 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 a 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 Duke University Medical Center institutional review board.

Sample

MCBS participants who were community dwelling at their index interview (file years 1999–2006), eligible for Medicare on the basis of age (≥65), and enrolled in fee-for-service Medicare were eligible. MCBS operates on a 4-year rotating panel design; individuals enter and leave the survey each year. Participants in this analysis contributed data for at least 1 year after their index interview to ascertain 12-month usage 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 nonwhite), highest education level (<high school, high school degree, ≥college), and marital status. Presence or absence of 13 health conditions was obtained according to self-report ("Have you ever been told that you have…?"): hypertension, arthritis (rheumatoid or nonrheumatoid), osteoporosis, diabetes mellitus, nonskin cancer, mental or psychiatric disorder, emphysema or chronic obstructive pulmonary disease, stroke, Alzheimer's disease, Parkinson's disease, heart arrhythmia, congestive heart failure, and coronary heart disease, which included myocardial infarction, heart attack, angina pectoris, and coronary heart disease.

Dates and types of health service use were identified in Centers for Medicare and Medicaid Services 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 developed to determine the optimal number of latent classes to fit the data. The Bayesian Information Criterion (BIC) reflects the likelihood function (how well the model predicts the data) and the number of parameters in the model. Models with smaller BIC values are preferable. Candidate model BICs were compared, and substantive interpretability and clinical judgment were used. (Do the classes that a given model defines have clinical significance or meaning?)

After selecting a latent class model, each participant was assigned 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 Latent Gold (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, secondary exploratory analyses were pursued for two purposes, first to determine whether, by altering the observed variable set used to "train" the LCA model, a superior set of latent multimorbidity classes could be derived that provided better data fit and improved entropy while retaining disease clusters that were clinically meaningful, and second to compare the predictive ability of latent class membership with the predictive ability of a simple count of chronic conditions. In regression models in which the usage outcomes were the dependent variables, models in which the primary independent variable was latent class membership or a simple morbidity count and models that included both independent variables were compared.

RESULTS

Determining the Optimal Number of Latent Classes

The smallest (most optimal) BIC values were obtained for the five- (BIC 151950) and six-class (BIC 151937)

Table 1. Characteristics of Persons Assigned to Six Multimorbidity Classes

Characteristic	Total Sample, N = 14,052	Minimal Disease, n = 4,613, 32.8%	Nonvascular, n = 3,509, 25.0%	Vascular, n = 3,211, 22.9%	Cardio-Stroke-Cancer, n = 1,165, 8.3%	Neurological Disease, n = 396, 2.8%	Very Sick, n = 1,158, 8.2%
Age, mean±SD	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
Male, %	43.5	52.7	23.8	46.3	64.4	39.1	38.5
White, %	86.8	88.1	90.3	81.0	89.9	81.1	86.1
Highest education level, %							
<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	19.8	23.4	19.2	18.3	19.9	14.4	13.0
Married, %	53.9	61.0	47.9	53.0	59.8	45.2	44.0
Number of 13 diagnoses, mean±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
Comorbidities							
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 disorder	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
Chronic obstructive pulmonary disease	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 mellitus	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
Coronary heart disease	25.3	5.4	15.0	25.6	74.0	33.8	83.3
Congestive heart failure	7.3	0	1.0	0	31.5	3.3	52.9

SD = standard deviation.

candidate models. Because the difference in BIC values between the five- and six-class models was so small, the merits of both models were considered. The six-class model was selected for the next steps in the primary analysis (Appendix S1).

The six classes were labeled based on which conditions had excess prevalence (prevalence in class exceeds prevalence in full cohort): Minimal Disease Class (prevalence of all conditions is below cohort average), Nonvascular Class (excess prevalence in cancer, osteoporosis, arthritis, arrhythmia, chronic obstructive pulmonary disease, psychiatric disorders), Vascular Class (excess prevalence in hypertension, diabetes mellitus, stroke), Cardio-Stroke-Cancer Class (excess prevalence in congestive heart failure, coronary heart disease, arrhythmia, stroke, and to a lesser extent hypertension, diabetes mellitus, cancer), Major Neurological Disease Class (excess prevalence in Alzheimer's disease, 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 their highest calculated probability of membership. Demographic characteristics and health status for each class are displayed in Table 1. The Minimal Disease Class was the largest group (32.7% of cohort), and most members had zero or one condition and tended to be younger and more educated. Individuals in other classes had varying degrees of multimorbidity, ranging from a mean of 2.8 conditions in the Nonvascular Class to 6.3 in the Very Sick Class. Age ranges were similar across classes (75.5–77.6), with the exception of the Major Neurological Disease Class (mean age 80.7 ± 7.7), in which almost nine in 10 members reported Alzheimer's disease. The proportion of men was highest in the Cardio-Stroke-Cancer Class, and the proportion of women was highest in the Nonvascular Class. The Very Sick Class was demographically similar to the Major Neurological Disease Class, although Very Sick Class members were typically younger (77.0 ± 7.6).

Relationship Between Multimorbidity Class Membership and Outcomes

The odds of hospital admission and ED use over a 1-year period are displayed in Figure 1 according to multimorbidity class. The Minimal Disease Class was used as the reference group, because its members had the lowest odds of use. In 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 use were higher in classes with higher disease burden. The highest odds of use were in the Very Sick Class (ED use: adjusted odds ratio (aOR) = 3.2, 95% confidence interval (CI) = 2.7–3.7; hospitalization: aOR = 5.2, 95% CI = 4.4–6.1).

Model Fit and Misclassification Error

Misclassification error was estimated at 0.36 for the sample. In other words, approximately one in three

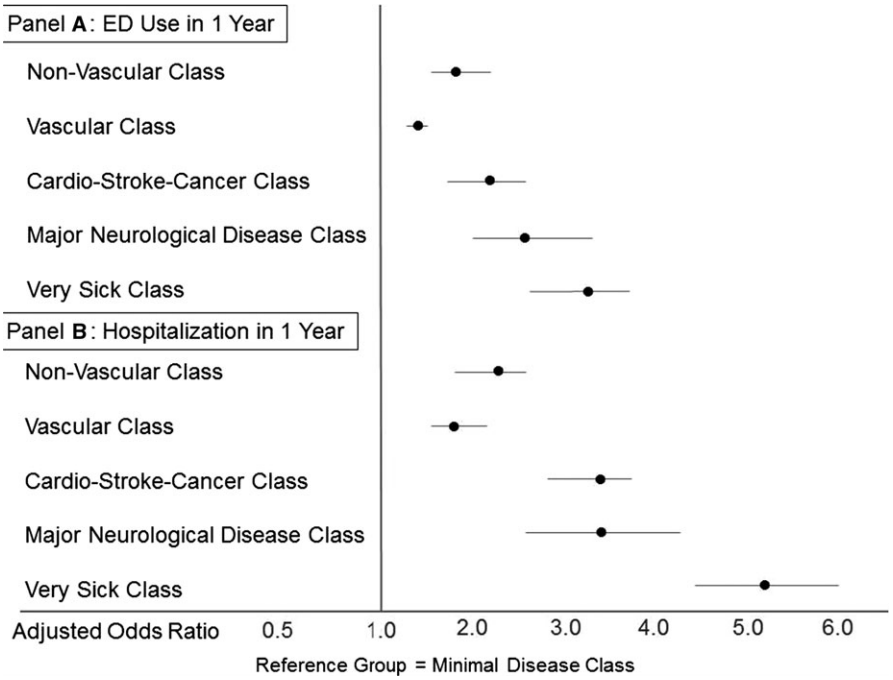

Figure 1. Odds of acute care use according to multimorbidity class. In logistic regression models that were adjusted for age, race, sex and education level, membership in any one of the "multimorbidity classes" was associated with higher odds of emergency department (ED) use and hospitalization over 1 year than membership in the minimal disease class.

participants had a pattern of multimorbidity that was a poor fit for any class or was similarly probable in multiple classes. Of the 14,052 participants, only 5,628 (40.1%) had 0.70 or greater calculated probability of membership in the best-fit class to which they were assigned; 11,781 (83.4%) had 0.40 or greater 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, number of chronic conditions was first added as a 14th observed variable. This strategy produced models with negligible misclassification error (estimate < 0.01), but comorbidity count, rather than patterns of disease co-occurrence, defined the latent classes almost entirely. Judging according to BIC values alone, the two-class model was optimal and sorted participants into a low (0–2 conditions) or high (3–11 conditions) disease prevalence class, with no overlap.

Next, LCA models were estimated using fewer indicator variables. Hypertension, osteoporosis, and psychiatric disorders were first eliminated because hypertension and osteoporosis were not strong independent predictors of the outcomes and because, by eliminating psychiatric disorders, the analysis focused on medical comorbidities. Arthritis, cancer, and diabetes were then eliminated, based on relatively weak independent relationships with use outcomes. In LCA models based on seven or 10 indicator variables, misclassification error remained high.

Comparison Between Multimorbidity Class and Simple Disease Count as Predictors of Outcomes

Table 2 summarizes the predictive power of multiply 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 use outcomes regardless of whether the multimorbidity indicators were multimorbidity class membership (Model 1), a simple count of diseases (Model 2), or both (Model 3). For the outcome of ED use, morbidity count remained a significant independent predictor ($P < .001$) in Model 3, whereas the significance of class membership as an independent predictor decreased ($P = .05$).

DISCUSSION

To the knowledge of the authors, this is the first study to characterize broad patterns of multimorbidity clusters empirically 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. The application of these empirically derived classes to individuals is challenging. The models had high misclassification error, indicating that many participants with multimorbidity could not be confidently assigned to a group. Although the recognition of major patterns of disease co-occurrence may help in organizing prevention and treatment initiatives, a simple count of

Table 2. Regression Models with Different Multimorbidity Indicators as Predictors of Acute Care Use

	Emergency Department Visit in 1 Year				Hospital Admission in 1 Year			
Model	*df*	Wald Chi-Square	*P*-Value	C-Statistic[a]	*df*	Wald Chi-Square	*P*-Value	C-Statistic
1: Multimorbidity class	5	260.5	<.001	0.627	5	470.0	<.001	0.667
2: Morbidity count	1	325.1	<.001	0.639[b]	1	533.3	<.001	0.678[b]
3								
Multimorbidity class	5	10.9	.05	0.640[b]	5	32.4	<.001	0.682[b]
Morbidity count	1	74.9	<.001		1	94.4	<.001	

All models adjusted for age, race, sex, education level.

df = degrees of freedom.

[a] The c-statistics for Models 2 and 3 were the same regardless of whether "morbidity count" was treated as a continuous or a 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 six levels.

[b] C-statistic is significantly different ($P < .001$) from the c-statistic for Model 1, as assessed using the DeLong test.[19] C-statistics of Models 2 and 3 were not significantly different from each other ($P = .86$ for outcome of ED visits; $P = .17$ for outcome of hospital admission).

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. Latent classes were identified based on co-occurrence in 32 medical, psychiatric, and deployment-specific conditions in 191,797 veterans.[15] The younger veteran population had a spectrum of disease that was significantly different from that of Medicare beneficiaries, including prevalent posttraumatic stress disorder, pain, traumatic brain injury, and substance abuse. The analysis also derived a model with six classes, the largest of which had minimal disease burden (53% of cohort).[15] A second study used several analytical approaches, including cluster analysis, principal components analysis, and LCA, to describe patterns or clusters of 10 conditions in 4,574 older Australians.[16] LCA yielded a four-class model, and the largest group was again a group with minimal disease (55.5% of cohort). The other three groups in that study resembled the current study's Nonvascular Class (high arthritis, asthma, depression), Vascular Class (high diabetes mellitus, hypertension), and Cardio-Stroke-Cancer Class (high heart disease, stroke, cancer).[16] Neither study[15,16] 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 previous study[16] supports the existence of broad disease clustering patterns in older adults. The patterns reflect plausible disease clusters that share similar underlying etiologies or risk factors. For example, the Vascular Class is characterized by diabetes mellitus and hypertension, which are part of the metabolic syndrome and are known risk factors for vascular disease.[17] The older Cardio-Stroke-Cancer Class may implicate shared risk factors for cancer and vasculopathy (e.g., smoking).

A previous study constructed LCA models based on 27 clinical features to identify phenotypes of people with heart failure.[18] The 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 other than comorbidity might improve identification of important phenotypes in persons aging with multimorbidity.

The current 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. Factors not controlled for may confound the relationships described. The analysis excluded long-term care residents and did not address health outcomes other than use.

Nonetheless, this study is a novel application of LCA to identify patterns of multimorbidity in a representative sample of Medicare beneficiaries. Six classes of disease co-occurrence emerged, and these multimorbidity patterns were clinically recognizable and theoretically plausible. The fact that many persons with multimorbidity do not fit neatly into one of the six classes limits application to decision-making in individuals. 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 subgroups or phenotypes in older populations should consider and report model entropy and misclassification error.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1: Selection of Optimal Latent Class Model.

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