

## RESEARCH ARTICLE

## Multimorbidity patterns and their relationship to mortality in the US older adult population

D. Diane Zheng<sup>1,2\*</sup>, David A. Loewenstein<sup>1</sup>, Sharon L. Christ<sup>3</sup>, Daniel J. Feaster<sup>2</sup>, Byron L. Lam<sup>4</sup>, Kathryn E. McCollister<sup>2</sup>, Rosie E. Curiel-Cid<sup>1</sup>, David J. Lee<sup>2</sup>

**1** Department of Psychiatry and Behavioral Science, Center for Cognitive Neurosciences & Aging, University of Miami Miller School of Medicine, Miami, Florida, United States of America, **2** Department of Public Health Sciences, University of Miami Miller School of Medicine, Miami, Florida, United States of America, **3** Department of Human Development and Family Studies and Statistics, Purdue University, West Lafayette, Indiana, United States of America, **4** Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, Florida, United States of America

\* [dzheng@med.miami.edu](mailto:dzheng@med.miami.edu)

## Abstract

## OPEN ACCESS

**Citation:** Zheng DD, Loewenstein DA, Christ SL, Feaster DJ, Lam BL, McCollister KE, et al. (2021) Multimorbidity patterns and their relationship to mortality in the US older adult population. PLoS ONE 16(1): e0245053. <https://doi.org/10.1371/journal.pone.0245053>

**Editor:** Kenzie Latham-Mintus, Indiana University Purdue University at Indianapolis, UNITED STATES

**Received:** July 29, 2020

**Accepted:** December 21, 2020

**Published:** January 20, 2021

**Copyright:** © 2021 Zheng et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Data Availability Statement:** The data used by this research is available at the National Center for Health Statistics, National Health Interview Survey website: [https://www.cdc.gov/nchs/nhis/nhis\\_questionnaires.htm](https://www.cdc.gov/nchs/nhis/nhis_questionnaires.htm).

**Funding:** This work was supported grants from National Eye Institute (F31EY025936 DDZ); and National Institute on Aging (R01AG061106 DAL and R01AG055638 REC). The organization that provided funding had no role in the design and conduct of the study; management, analysis, and

## Background

Understanding patterns of multimorbidity in the US older adult population and their relationship with mortality is important for reducing healthcare utilization and improving health. Previous investigations measured multimorbidity as counts of conditions rather than specific combination of conditions.

## Methods

This cross-sectional study with longitudinal mortality follow-up employed latent class analysis (LCA) to develop clinically meaningful subgroups of participants aged 50 and older with different combinations of 13 chronic conditions from the National Health Interview Survey 2002–2014. Mortality linkage with National Death Index was performed through December 2015 for 166,126 participants. Survival analyses were conducted to assess the relationships between LCA classes and all-cause mortality and cause specific mortalities.

## Results

LCA identified five multimorbidity groups with primary characteristics: “healthy” (51.5%), “age-associated chronic conditions” (33.6%), “respiratory conditions” (7.3%), “cognitively impaired” (4.3%) and “complex cardiometabolic” (3.2%). Covariate-adjusted survival analysis indicated “complex cardiometabolic” class had the highest mortality with a Hazard Ratio (HR) of 5.30, 99.5% CI [4.52, 6.22]; followed by “cognitively impaired” class (3.34 [2.93, 3.81]); “respiratory condition” class (2.14 [1.87, 2.46]); and “age-associated chronic conditions” class (1.81 [1.66, 1.98]). Patterns of multimorbidity classes were strongly associated with the primary underlying cause of death. The “cognitively impaired” class reported similar number of conditions compared to the “respiratory condition” class but had significantly higher mortality (3.8 vs 3.7 conditions, HR = 1.56 [1.32, 1.85]).

interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

**Competing interests:** The authors have declared that no competing interests exist.

## Conclusion

We demonstrated that LCA method is effective in classifying clinically meaningful multimorbidity subgroup. Specific combinations of conditions including cognitive impairment and depressive symptoms have a substantial detrimental impact on the mortality of older adults. The numbers of chronic conditions experienced by older adults is not always proportional to mortality risk. Our findings provide valuable information for identifying high risk older adults with multimorbidity to facilitate early intervention to treat chronic conditions and reduce mortality.

## Introduction

Advances in modern medicine have substantially increased life expectancy, as a result, more people are living into old age and developing chronic conditions. Multimorbidity is the presence of two or more chronic health conditions in an individual [1]. In the United States, the number of older adults living with multimorbidity has increased rapidly [2]. According to a report by RAND, 81% of Americans 65 years and older and 50% aged 45 to 65 years had multiple chronic conditions [3]. In a study of Medicare beneficiaries, 64% of participants had two or more conditions and 24% had four or more [4]. The prevalence of multi-morbidity also has increased in other regions of the world over the past 20 years, and is anticipated to continue rising [2,5,6]. Multi-morbidity is associated with poor daily functioning, increased psychological distress and disability, higher medical utilization and reduced quality of life [4,7,8]. The prevalence of multi-morbidity increases with age [9]. Approximately 71% of US total health care spending is for the treatment of patients with multi-morbidity [10].

Studies have linked multimorbidity to increased risk of mortality [11], but the results are inconclusive [11–17] and most studies had relatively small samples. Previous studies have measured multimorbidity as a cumulative count of conditions or a combination of count and severity of diseases (i.e., Charleston comorbidity index) rather than a qualitative combination of conditions. Multimorbidity increases the risk of adverse consequences to the physiological system from potential interactions between the morbidities and disease treatment. Clusters of conditions may have a synergistic effect on disability or mortality. Investigating chronic condition combination types is crucial in understanding the effect of multi-morbidity on health and mortality.

Latent class analysis (LCA) is a data driven statistical approach that classifies individuals into homogeneous subgroups based on their pattern of response across several observed variables such that individuals within a group are more similar than individuals between groups. Therefore, LCA can be effectively used to determine distinct multimorbidity combination types [18]. Although LCA has been performed to evaluate multimorbidity in various populations [19–24], to our knowledge, LCA has not been applied in examining the multimorbidity combination types and their relationship to mortality in a national representative sample of community residing US older adults. The purpose of this study was to employ LCA techniques to identify patterns of multimorbidity in the US 50 years and older population and evaluate their relationships with all-cause and cause-specific mortalities by utilizing the recent linkage between the National Health Interview Survey (NHIS) and the National Death Index (NDI) [25].

## Methods

### Data source

This cross-sectional study with longitudinal mortality follow-up utilized data from NHIS 2002 to 2014. NHIS is an annual, cross-sectional survey of US civilian non-institutionalized

population conducted by the National Center for Health Statistics (NCHS) [26]. Each year NHIS samples near 35,000 households with estimated 87,500 persons with an oversampling of black, Hispanic, Asian and adults 65 years or older [26]. The NHIS sampling follows a multi-purpose multistage area probability design; therefore data, when properly weighted, is representative of the US population [27]. A core set of questions is asked each year, and data can be pooled across years to enhance sample size [28]. The response rates for NHIS during the study period range from 73.8% to 89.6%. Participants aged 50 years and older were included in this investigation.

### Chronic conditions

Thirteen chronic conditions were included for the analysis: hypertension, coronary artery disease, other heart diseases, stroke, emphysema/COPD, asthma, cancer, diabetes, arthritis, kidney disease, hepatitis, depressive symptoms, and cognitive impairment. The conditions were selected based on the chronic condition list established by the US Department of Health and Human Services (DHHS) Initiative on Multiple Chronic Conditions (MCC) [29,30], which were available in NHIS. Participants were asked: Have you EVER been told by a doctor that you had. . . (i.e. hypertension, also called high blood pressure)? Coronary heart disease, angina pectoris, and myocardial infarction were placed into a category called “coronary artery diseases”. The kidney disease information was collected by asking “during the past 12 months, have you been told by a doctor that you had weak or failing kidneys?”.

Cognitive impairment was measured by the following question: “Are you limited in any way because of difficulty remembering or because experience periods of confusion?” Those who answered “yes” were categorized as “cognitively impaired”. This measure has been shown to produce cognitive impairment prevalence that are similar to estimates from using more precise case-ascertainment methods [31,32]. Depressive symptoms were assessed by using four of the six items from the Kessler-6 nonspecific psychological distress scale: “During the past 30 days how often do you feel (1) sad nothing could cheer you up, (2) hopeless, (3) that everything was an effort, (4) worthless?” [33,34] Responses were recorded on a 5 point scale ranging from 0 (none of the time) to 4 (all of the time) with a sum score above 8 considered having depressive symptoms [35]. The 8-point cutoff of the sum of 4 items is equivalent to the 12-point cutoff point for severe mental illness on sum of 6 items [33,35,36]

### Mortality linkage

NHIS data was linked with National Death Index (NDI) through probabilistic record matching using name, social security number, date of birth, state of residence, sex, race, and marital status. Vital status was obtained with date of death, and underlying causes of death if participants were deceased. We used the public-use linked mortality file which, for selected records, the date of death and/or underlying cause of death were subjected to data perturbation for privacy protection. The mortality follow-up was performed from the date of survey through December 31, 2015 [37]. 172,030 participants aged 50 years and older were involved in NHIS, of whom 166,126 (96.6%) had sufficient identification information to be linked with NDI for mortality follow-up. Our study examined all-cause mortality, and cause-specific mortalities due to cancer (ICD-10: C00-C97), heart diseases (I00-I09, I11, I13, I20-I51), cerebrovascular disease (I60-I69), chronic lower respiratory diseases (J40-J47), and Alzheimer’s Disease (G30).

The University of Miami Institutional review board approved this study and exempted the patient consent form requirement because the study was a secondary analysis of publicly available de-identified data.

## Covariates

The socio-demographic variables examined included age in years, sex (female vs. male), race (Black, Asian, other races vs. White), Hispanic background (vs. non-Hispanic), education level (high school graduate, above high school vs. less than high school), marital status (married vs. all other), health insurance (vs. no insurance), and household income (income to poverty threshold ratio < 1 (poor), ratio 1–1.99 (low income), and ratio > 4 (high income) vs. ratio 2–3.99 (middle class)). Health behavior variables included: smoking status (current, former vs. never), alcohol drinking status (none, moderate, heavy vs. light), and BMI (underweight, overweight, obese vs. normal weight).

## Statistical analysis

A series of LCA models ranging from two to nine classes were estimated and compared. Model fit statistics included Akaike information criterion (AIC), Bayesian information criterion (BIC), sample-size adjusted BIC, for which smaller values of fit indices indicate a better model fit to the data. When a smallest value was not reached, a scree plot was utilized to select the optimal model. Entropy, an index summarizing the overall precision of the classification for all samples across classes, compared models. An entropy above 0.7 is considered a good value [38]. The Vuong-Lo-Mendell-Rubin and Lo-Mendell-Rubin likelihood ratio tests evaluated model improvement as the number of classes increased. The latent classes derived should have substantive clinical meaning and be distinct from each other. A parsimonious model is preferred when other indices are similar. LCA assumes that class indicators are conditionally independent of each other given class membership. We further examined the conditional independence with bivariate residuals (BVRs). Because BVRs are very sensitive to large sample size, we ordered the BVRs in descending order and allowed pairs with top bivariate residuals to correlate [39]. Participants were assigned to the class for which they had the highest probability of membership. Cross-tabulation of multimorbidity latent classes and socio-demographic and health behavior variables provided the characteristics of individuals in each class.

The multimorbidity latent class was used as a predictor of mortality. Cox proportional hazards models with the latent class as predictor and survival time as outcome were performed while controlling for covariates in the model. We examined the proportional hazard assumption by plotting the survival function over time. The survival curves that did not cross from each other indicating proportional hazard.

Introducing predictors or outcome variables to LCA models could potentially cause latent class shifts. We first estimated an unconditional LCA model and obtained the latent class and associated classification probabilities. During the regression steps, we adapted the manual three-step approaches [40] to minimize class shifts and adjust for potential bias when a latent class variable is used for prediction of distal outcome.

The LCA and survival analysis were performed using Mplus 8.0 (Muthén & Muthén). Descriptive statistics were calculated using SAS 9.4 (SAS Institute, Inc., Cary, NC) survey procedures. Analyses accounted for the complex survey design of NHIS with adjustments to the weight variable to account for the pooling of 13 years of data [27]. In the case of multiple comparisons, the  $\alpha$  value and corresponding confidence intervals were Bonferroni corrected.

## Results

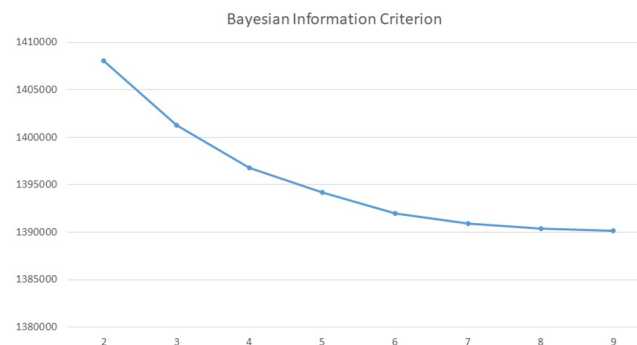
We utilized the study sample of 166,126 participants who had mortality follow-up information for all analyses. The study sample represents 89.2 million US adults aged 50 years and older. The average age of the sample was 64.9 years (SD 10.5) at the time of survey; 53.6% female, 82.9% White, 10.0% Black, 3.6% Asian, 3.5% other races. Hispanics made up 8.3% of the study

population and 52.7% had above high school education. Of the 13 conditions included in the LCA, the prevalence of hypertension was 51.3%, highest, followed by arthritis (41.5%), and diabetes (16.6%).

### Identifying latent class chronic condition patterns in the population

The model fit statistics improved as the number of classes increased, and a smallest value was not reached. Therefore, a scree plot was utilized to select the optimal number of classes (Fig 1). Minimum model improvement occurred beyond the five-class model, which had the highest entropy value of 0.64. The disease class identified by the 5-class model also represents clinically meaningful groups that share common underlying etiologies or risk factors. Therefore, the 5-class model was selected based on a combination of the model fit indices, parsimony, and clinical classification relevance. Upon examining the conditional independence of the 5-class model, we allowed the following pairs of conditions to correlate at the overall level—hypertension and diabetes, coronary artery disease and other heart diseases, coronary artery disease and stroke. We reached an improved 5-class model; the BIC value of the 5-class model with bivariate association is less than the BIC of both the 5 and 6 class models (Table 1).

Classes were labeled according to their characteristic of the chronic conditions (Fig 2 and Table 2): 1) “Healthy” class (51.5% of the sample) is characterized by lower probabilities (<10%) of reporting any chronic condition except hypertension (26%) and arthritis (22%).



**Fig 1. Scree plot of Bayesian information criteria (BIC) to select the optimal number of class model.**

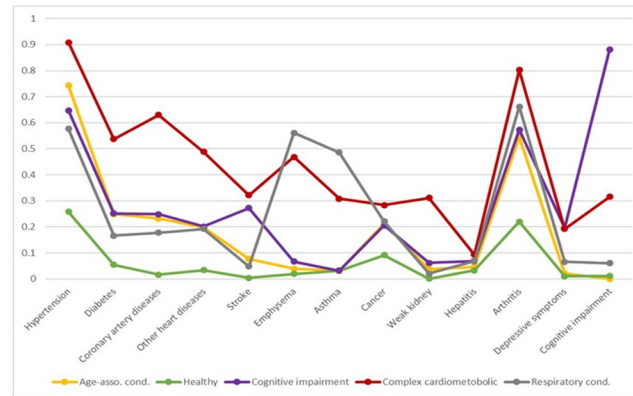
<https://doi.org/10.1371/journal.pone.0245053.g001>

**Table 1. Model fit statistics for latent class analysis.**

Number of latent class	Log Likelihood	Number of parameters	AIC*	BIC*	Adjusted BIC	Entropy
2	-703,854	27	1,407,763	1,408,033	1,407,948	0.603
3	-700,390	41	1,400,862	1,401,272	1,401,142	0.64
4	-698,057	55	1,396,225	1,396,776	1,396,602	0.57
5	-696,690	69	1,393,518	1,394,209	1,393,990	0.64
6	-695,475	83	1,391,116	1,391,948	1,391,684	0.628
7	-694,885	97	1,389,965	1,390,937	1,390,629	0.58
8	-694,539	111	1,389,301	1,390,414	1,390,061	0.596
9	-694,341	125	1,388,933	1,390,185	1,389,788	0.598
5 with BVR association	-695,250	72	1,390,645	1,391,367	1,391,138	0.64

\*AIC—Akaike information criterion, BIC—Bayesian information criterion.

<https://doi.org/10.1371/journal.pone.0245053.t001>



**Fig 2. Probabilities of having chronic conditions for each latent class.**

<https://doi.org/10.1371/journal.pone.0245053.g002>

Individuals in this class on average reported 0.7 conditions; 2) “Age-associated chronic conditions (hypertension & arthritis)” class (33.6%) is characterized by elevated risk of hypertension (74%) and arthritis (55%). Persons in this class had conditions that are often associated with aging and reported 2.8 conditions on average; 3) “Respiratory condition” class (7.3%) had high prevalence of emphysema/COPD (56%), asthma (49%) and arthritis (66%) and reported 3.7 conditions on average; 4) “Cognitively impaired” class (4.3%) displayed highly elevated risk of cognitive impairment (88%) and depressive symptoms (20%). This group also had high probability of having stroke (27%), hypertension (65%) and arthritis (57%) and 3.8 conditions on average; 5) “Complex cardiometabolic” class (3.2%) had the highest prevalence of hypertension (91%), diabetes (54%), coronary artery diseases (63%), other heart diseases (49%), stroke (32%), kidney disease (31%), cancer (28%) and arthritis (80%). On average, individuals in this group reported 6.5 conditions.

**Table 2. Probabilities of reporting chronic condition for each latent class.**

	Complex cardiometabolic	Cognitively impaired	Respiratory condition	Age-asso. cond.	Healthy
Hypertension	0.91	0.65	0.58	0.74	0.26
Diabetes	0.54	0.25	0.17	0.25	0.05
Coronary artery diseases	0.63	0.25	0.18	0.23	0.02
Other heart diseases	0.49	0.20	0.19	0.20	0.03
Stroke	0.32	0.27	0.05	0.08	0.00
Emphysema	0.47	0.07	0.56	0.04	0.02
Asthma	0.31	0.03	0.49	0.03	0.03
Cancer	0.28	0.21	0.22	0.21	0.09
Weak kidney	0.31	0.06	0.02	0.04	0.00
Hepatitis	0.09	0.07	0.07	0.05	0.03
Arthritis	0.80	0.57	0.66	0.55	0.22
Depressive symptoms	0.19	0.20	0.07	0.02	0.01
Cognitive impairment	0.32	0.88	0.06	0.00	0.01
Mean number of cond.	6.5	3.8	3.7	2.8	0.7
SD	1.2	1.3	1.1	0.9	0.6
N	5,304	7,223	12,163	55,853	85,583
%	3.2%	4.3%	7.3%	33.6%	51.5%

<https://doi.org/10.1371/journal.pone.0245053.t002>

The socio-demographic and health behavior factors distributed differently across the five latent classes as displayed in Table 3. The “healthy” class is younger (average age of 62.0 years) and better educated (58.1% above high school education), while the “complex cardiometabolic”, the “age associated condition” and the “cognitively-impaired” class were older (average age 68.0, 68.1 and 70.1); and the “complex cardiometabolic” and “cognitively-impaired” class were less educated (36.0% above high school education). The “respiratory condition” class had a high percentage of females (65.5%). The “healthy” and the “age-associated condition” class had a higher percentage of married individuals (66.4% and 61.0%); whereas only 41.2% in the “cognitively impaired” class were married. The “complex cardiometabolic” class had the highest percentage of obesity (46.2%) and former smokers (44.5%).

**Table 3. Distribution of demographic and health behavior variables by multimorbidity latent class\*.**

	Complex cardiometabolic (%)	Cognitively impaired (%)	Respiratory condition (%)	Age asso. conditions (%)	Healthy (%)	Total (%)
N	5,304	7,223	12,163	55,853	85,583	166,126
Age—Mean (SD)	68.0 (10.3)	70.1 (12.0)	65.7 (10.0)	68.1 (10.2)	62.0 (9.8)	64.9 (10.5)
Gender—Male	44.3	43.7	34.5	48.2	47.2	46.4
Female	55.7	56.3	65.5	51.8	52.8	53.6
Race—White	78.7	77.8	86.4	82.5	83.3	82.9
Black	14.3	14.6	9.4	11.5	8.6	10.0
Asian	2.3	3.0	1.4	2.8	4.5	3.6
All other races	4.6	4.6	2.8	3.2	3.6	3.5
Ethnicity-Hispanic	8.4	9.6	5.3	7.4	9.2	8.3
Non-Hispanic	91.6	90.7	94.7	92.6	90.8	91.7
Education < 12th grade	34.4	32.7	22.4	19.4	13.4	17.3
12th grade	30.0	31.3	31.9	32.1	28.5	30.1
Above 12th grade	36.0	36.0	45.8	48.5	58.1	52.7
Marital status-Married	47.4	41.2	54.9	61.0	66.4	62.3
All other	52.6	58.8	46.0	39.0	33.6	37.7
Had health insurance	96.0	94.9	93.5	94.9	90.0	92.2
No insurance	4.0	5.1	6.5	5.1	10.0	7.8
Income to poverty threshold ratio <1	25.8	23.7	15.2	10.1	7.1	9.8
Ratio 1–1.99	31.3	28.8	22.6	20.2	13.5	17.4
Ratio 2–3.99	28.4	29.3	31.8	31.8	28.0	29.5
Ratio 4 or +	14.5	18.3	30.4	37.9	51.5	43.3
Smoking—Never smoker	33.6	48.0	35.1	49.0	55.0	50.8
Current Smoker	21.9	17.2	24.2	12.5	16.0	15.7
Former Smoker	44.5	34.8	40.7	38.5	29.0	33.6
Drinking- Abstainer	68.5	65.2	49.3	48.0	36.6	43.2
Light drinker	24.5	24.1	36.0	35.1	41.7	38.0
Moderate drinker	5.0	7.4	9.7	12.7	16.4	14.1
Heavy drinker	2.1	3.3	5.0	4.2	5.3	4.7
BMI—Underweight	2.2	3.9	2.9	1.1	1.5	1.5
Normal weight	20.2	36.8	26.3	24.0	37.3	31.7
Overweight	31.4	31.3	31.1	37.6	39.8	37.9
Obese	46.2	28.0	39.7	37.2	21.4	28.8

\*All p values of  $\chi^2$  test are < 0.001. Percentages may not appear to add up to 100% due to rounding.

<https://doi.org/10.1371/journal.pone.0245053.t003>



## The association between multimorbidity class and mortality

**a) All-cause mortality.** The average mortality follow-up time was 6.49 years (range <1 to 14 years); 28,129 (16.9%) deaths were observed. Cox proportional hazard model adjusting for covariates indicated participants in different multimorbidity classes had various elevated mortality risks compared to the “healthy” class. The “complex cardiometabolic” class had the highest mortality with a hazard ratio (HR) of 5.30 and a 99.5% confidence interval (CI) of [4.52, 6.22]; followed by the “cognitively impaired” class (HR 3.34 [2.93, 3.81]); the “respiratory condition” class (2.14 [1.87, 2.46]); and the “age-associated chronic condition” class (1.81 [1.66, 1.98]). (All  $P < 0.001$ ). (Table 4, Fig 3) The  $\alpha$  and confidence intervals were Bonferroni corrected for 10 comparisons ( $0.05/10 = 0.005$ ).

Pairwise comparisons of mortality risk among the multimorbidity classes also showed statistically significant differences. The mortality risk of the “complex cardiometabolic” class was 1.59 times higher than the “cognitively impaired” class (HR 1.59, 99.5% CI [1.27, 1.98], “complex cardiometabolic” vs. “cognitive impaired”,  $P < .001$ ). The “cognitively impaired” class had a 56% higher risk of dying than the “respiratory condition” class (HR 1.56, 99.5% CI [1.32, 1.85], “Cognitively impaired” vs. “Respiratory condition”,  $P < 0.001$ ). (Table 4).

**b) Cause-specific mortalities (Table 5).** Cox proportional hazard model adjusting for study design and covariates indicated **heart disease** mortality was drastically elevated in the “complex cardiometabolic” class (HR 7.41, 95% CI [6.06, 9.05],  $P < 0.001$ ) compared to “healthy” class. The “cognitively impaired” class (HR 3.58 [2.86, 4.48],  $P < 0.001$ ) and the “age-associated condition” class (HR 2.88 [2.46, 3.37],  $P < 0.001$ ) were also associated with increased risk for heart disease death but not the “respiratory-arthritis” class (HR 1.20 [0.82, 1.75],  $P = 0.35$ ).

The “complex cardiometabolic” class (HR 4.94 [3.23, 7.57]), the “cognitively impaired” class (HR 4.66 [3.42, 6.53]), and the “age-associated condition (hypertension-arthritis)” class (HR 2.26 [1.69, 3.02]) all had heightened **cerebrovascular disease** mortality risk compared to “healthy” class (all  $P < 0.001$ ). The “respiratory condition” class did not show an increased cerebrovascular mortality risk (HR 0.96 [0.45, 2.05],  $P = 0.92$ ).

The “respiratory condition” class (HR 13.65 [10.82, 17.24]) and the “complex cardiometabolic” (HR 8.34 [6.10, 11.39]) had substantially increased **chronic lower respiratory disease** mortality risk compared to the “healthy” class. The “age associated condition” class (HR 0.50

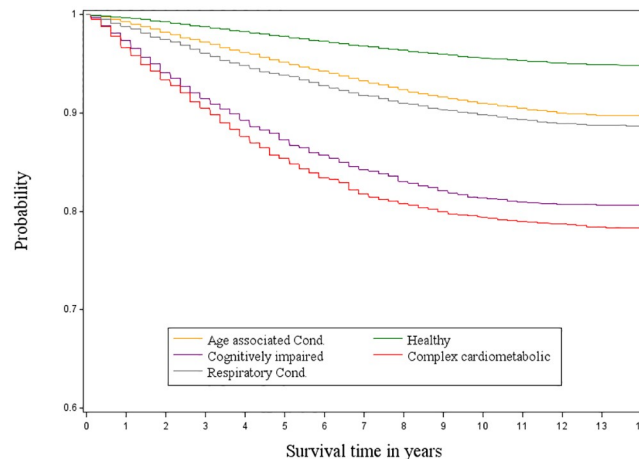
**Table 4. Hazard ratios of all-cause mortality controlled for covariates\*.**

Multi-morbidity classes	Hazard Ratio	99.5% Confidence Interval	P value
Healthy	1.00		
Age-associated conditions (1)	1.81	[1.66, 1.98]	<0.001
Respiratory conditions (2)	2.14	[1.87, 2.46]	<0.001
Cognitively impaired (3)	3.34	[2.93, 3.81]	<0.001
Complex cardiometabolic (4)	5.30	[4.52, 6.22]	<0.001
C-cardiometabolic (4) vs. Cognitive impaired (3)	1.59	[1.27, 1.98]	<0.001
C-cardiometabolic (4) vs. Respiratory (2)	2.48	[1.98, 3.10]	<0.001
C-cardiometabolic (4) vs. Age asso. (1)	2.93	[2.46, 3.49]	<0.001
Cognitive impaired (3) vs. Respiratory (2)	1.56	[1.32, 1.85]	<0.001
Cognitive impaired (3) vs. Age asso. (1)	1.85	[1.63, 2.09]	<0.001
Respiratory cond. (2) vs. Age asso. (1)	1.18	[1.03, 1.36]	0.001

\* Model controlled for age, sex, race, education, Hispanic ethnicity, marital status, household income, smoking status, drinking status, health insurance and BMI category.

<https://doi.org/10.1371/journal.pone.0245053.t004>





**Fig 3. Kaplan-Meier survival curves of latent classes for all-cause mortality.**

<https://doi.org/10.1371/journal.pone.0245053.g003>

[0.29, 0.86],  $P < 0.001$ ) and the “cognitively impaired” class (HR 0.90 [0.37, 2.18],  $P = 0.82$ ) did not show increased respiratory disease mortality.

The “cognitively impaired” class had elevated risk of **Alzheimer’s Disease** death (HR 6.27 [4.74, 8.28],  $P < 0.001$ ). The other three disease classes did not have elevated risk of Alzheimer’s disease death compared to the “healthy” class.

All four multimorbidity classes were associated with an increased risk for **cancer** mortality: “complex cardiometabolic” class (HR 2.23 [1.82, 2.74]), “cognitively impaired” class (HR 1.89 [1.59, 2.26]), “age-associated condition” class (HR 1.58 [1.41, 1.78]) “respiratory condition” class (HR 1.87 [1.59, 2.19]), and compared to “healthy” class (all  $P < 0.001$ ).

**Table 5. Hazard ratios of cause-specific mortalities for each multimorbidity class\*.**

Multi-morbidity Class	Heart diseases death	Cerebrovascular disease death	Chronic lower respiratory disease death	Alzheimer’s disease death	Cancer death
	Hazard ratio	Hazard ratio	Hazard ratio	Hazard ratio	Hazard ratio
	95% CI	95% CI	95% CI	95% CI	95% CI
	P value	P value	P value	P value	P value
<b>No. of Deaths</b>	4754	1429	1642	773	6996
<b>Healthy group</b>	1.00	1.00	1.00	1.00	1.00
<b>Complex cardio-metabolic</b>	7.41	4.94	8.34	1.62	2.23
	[6.06, 9.05]	[3.23, 7.57]	[6.10, 11.39]	[0.81, 3.24]	[1.82, 2.74]
	<.001	<.001	<.001	0.17	<.001
<b>Cognitively impaired</b>	3.58	4.66	0.90	6.27	1.89
	[2.86, 4.48]	[3.42, 6.35]	[0.37, 2.18]	[4.74, 8.28]	[1.59, 2.26]
	<.001	<.001	0.82	<.001	<.001
<b>Age-associated conditions</b>	2.88	2.26	0.50	0.48	1.58
	[2.46, 3.37]	[1.69, 3.02]	[0.29, 0.86]	[0.31, 0.76]	[1.41, 1.78]
	<.001	<.001	0.012	0.002	<.001
<b>Respiratory condition</b>	1.20	0.96	13.65	0.08	1.87
	[0.82, 1.75]	[0.45, 2.05]	[10.82, 17.24]	[0.00, 7.00]	[1.59, 2.19]
	0.35	0.92	<.001	0.27	<.001

\*Models adjusted for age, sex, race, Hispanic ethnicity, education, income, health insurance, smoking status, alcohol drinking status and BMI.

<https://doi.org/10.1371/journal.pone.0245053.t005>

## Discussion

Our study is the first to investigate the relationship between the multimorbidity combination types and mortality in the U.S. older adult population using an innovative LCA approach. LCA reduced the complexity of data and identified five distinct meaningful subgroups in older adults: “healthy,” “age-associated chronic conditions,” “respiratory condition,” “cognitively impaired,” and “complex cardiometabolic.” We found four multimorbidity classes had various levels of elevated mortality risk, and the patterns of multimorbidity classes were strongly associated with the primary underlying cause of death. Additionally, the number of chronic conditions older adults experienced were not always proportional to the mortality risk they suffer.

Other studies that investigated the relationship between multimorbidity and mortality in older adults have measured multimorbidity as merely a cumulative count of conditions; these studies found dose-response positive relationships between numbers of conditions and the increased mortality risk [11,12,14]. Our study goes beyond measuring multi-morbidity as a count of conditions or arbitrary grouping. Instead, we employed the data driven LCA methodology and characterize the population into qualitatively distinct groups based on the relationship among the conditions.

Numbers of conditions is a straightforward and useful way of measuring multimorbidity. However, it weighs the impact of conditions equally. As our results show, groups reporting similar number of conditions can have significantly different mortality rates depending on the combinations of conditions. The “cognitively impaired” class reported on average 3.8 conditions, which was similar to the “respiratory condition” class who reported 3.7 conditions on average; however, the “cognitively impaired” class had a 56% higher all-causes mortality risk than the “respiratory condition” class (HR 1.56 [1.32, 1.85],  $P < 0.001$ ). These findings suggest certain chronic condition combinations such as cognitive impairment and depressive symptoms, had a substantial detrimental effect on overall mortality in older adults.

The “cognitively impaired” class had an 88% chance of having cognitive impairment which is considerably higher than other classes. This class also had a 20% chance of reporting depressive symptoms and 27% of stroke. Cognitive impairment has been shown to be an independent predictor of mortality in older adults even after controlling for multiple confounders [41]. Increased mortality was found even for very mild level of cognitive impairment [42]. Depression is associated with increased mortality in older persons and is a risk factor for Alzheimer’s Disease (AD) [43]. The prevalence of multimorbidity in older adults exceeds 60% [7]. A single cause of death may not capture the full range of diseases that older adults endured at the end of life. Our data show the conditions that frequently co-occurred with cognitive-impairment and depressive symptom includes stroke, cancer, arthritis and hypertension. The physiological health of the “cognitively impaired-depressive symptoms” class were not as severe as indicated by the relatively moderate number of conditions reported (3.8). However, cognitive impairment and depressive symptoms are debilitating conditions that affect the daily life of older adults and can cause increased disability and dependency on others [44,45], and prevented them from seeking proper medical care and adhering to proper disease management [46,47]. These could exacerbate older adults’ health situation and increase mortality risk.

The “complex cardiometabolic” class was not the oldest group identified in the study; the average age was 68.0 compared to 68.1 of “age associated condition” and 70.1 of “cognitively impaired”. However, this group had the highest mortality risk. The risk of dying in the “complex cardiometabolic” class was almost 3 times higher than the “age associated condition” class (HR 2.93,  $P < 0.001$ ) and 59% higher than the “cognitively impaired” class (HR 1.59,  $P < 0.001$ ). In addition to having the highest prevalence for 9 out of the 13 chronic conditions, the “complex cardiometabolic” class was also the least educated, had the lowest income, and

was most likely to be obese or former smoker among all classes (Table 3). These socio-economic disadvantages and poor lifestyle factors may have synergized with multiple chronic conditions and led to the highly increased mortality risk of the “complex cardiometabolic” class.

It was challenging to come up with names that summarized the condition of each multimorbidity class while still being succinct. For example, arthritis and hypertension were the two most common conditions in this age group with high prevalence in all four multimorbidity classes. We did not feel it was informative to include arthritis and hypertension in the name of all disease classes. Instead, we aimed to highlight the conditions that are not only most prevalent in a class but also distinct from other classes. However, the fact that arthritis and hypertension were a component of many of the disease classes, raises the possibility that underlying cerebrovascular disease or inflammatory response may relate to comorbid conditions and is an area of future research.

Our analysis of the cause-specific mortality demonstrated the patterns of multimorbidity classes were strongly associated with the primary underlying cause of death. The “complex cardiometabolic” class had the highest risk of heart disease death; and the “respiratory condition” class had the highest risk of chronic lower respiratory disease death. The “cognitive impaired” class had the highest risk of Alzheimer’s Disease mortality. Both the “cognitive-impaired” and the “complex cardiometabolic” classes had the highest risk of cerebrovascular disease death. This alignment of the primary underlying cause of death in each multimorbidity class confirms the categorization and naming of our multi-morbidity latent classes.

Although the percent of participants who were ineligible for mortality follow-up was very low (3.4%), we conducted analyses to determine if selection bias occurred during mortality follow-up, specifically whether the mortality follow-up ineligibility influenced one multi-morbidity class more than the other. The percentage follow-up ineligibility was the highest in the “healthy” class (4.2%), and lowest in the “complex cardiometabolic” class (1.8%) with the other three classes in the middle. Given the large sample size of the “healthy” class (over 88,500) and its health condition homogeneity (low prevalence in most conditions), the influence of mortality follow-up ineligibility bias was likely minimal. Therefore, for consistence reason, we utilized the study samples (96.6%,  $n = 166,126$ ) who had mortality follow-up information for both the LCA analysis and the survival analysis.

One weakness of using LCA to study the multimorbidity in older adult population is the precision of the classification. The entropy which measures the precision of the classification of LCA models was only 0.64 and did not reach the ideal values of above 0.7. In contrast to our previous study which used NHIS data to examine multimorbidity patterns in the US general adult (age  $\geq 18$ ) population [48], an entropy value of 0.72 was achieved. Such reduction in classification precision have been reported [22] and is likely due to more heterogeneity in chronic condition patterns among older adults. This may be analogous to the phenomenon of reduced predictive utility of traditional risk factors in the older population. [49]. Other limitations include NHIS data were self-reported and subjective to recall bias. Only 14 of the 20 chronic conditions in the DHHS list [29,30] were available in NHIS data (“congestive heart failure” and “cardiac arrhythmias” were combined in “any other heart conditions” thus 14 instead of 13). The conditions that were not available in NHIS including autism, HIV, osteoporosis, schizophrenia, and substance abuse. Hyperlipidemia was only collected in some years of NHIS. Some of these conditions, such as autism, are not prevalent in the older population. We believe our study included the most important chronic conditions that have a strong influence on older adult mortality. The reference periods for the 14 chronic conditions were not consistent in NHIS; however, all conditions are chronic in nature. For example, even though cognitive impairment questions were asking about current state, cognitive impairment in older

adult is generally a slow changing process, we believe the influence of the reference period on our study results is likely small.

Our investigation represents the first study to use national representative community-based data to study the pattern of multimorbidity combination type and mortality in the national level of US older adult population. The strength of the study includes large sample size, national representative data, and newly updated mortality linkage. It is expensive and difficult to evaluate a national sample by using standard validated cognitive-impairment ascertainment in a large population. The fact that the NHIS collects data from a representative sample of the US population annually with data linked to national death index makes it a powerful surveillance tool to study multimorbidity and mortality.

## Conclusions

Our study contributes to a better understanding of the effect of multimorbidity on the mortality in the US older adult population. Our findings provide valuable information for identifying vulnerable sub-populations such as the “complex cardiometabolic” and the “cognitively impaired” class who were at significantly increased risk of mortality. The results support an integrated and coordinated care system for older adults with multimorbidity to facilitate early intervention to prevent and treat related conditions. Our research suggests that primary care and geriatric physicians should pay close attention to signs of cognitive impairment and depressive symptoms in older patients. Even though they may not seem physiologically ill, these older adults face significantly heightened risk of mortality.

## Author Contributions

**Conceptualization:** D. Diane Zheng, Sharon L. Christ, David J. Lee.

**Data curation:** D. Diane Zheng.

**Formal analysis:** D. Diane Zheng.

**Funding acquisition:** D. Diane Zheng, David A. Loewenstein, Rosie E. Curiel-Cid.

**Methodology:** D. Diane Zheng, Sharon L. Christ, Daniel J. Feaster, Byron L. Lam, David J. Lee.

**Supervision:** David J. Lee.

**Writing – original draft:** D. Diane Zheng.

**Writing – review & editing:** D. Diane Zheng, David A. Loewenstein, Sharon L. Christ, Daniel J. Feaster, Byron L. Lam, Kathryn E. McCollister, Rosie E. Curiel-Cid, David J. Lee.

## References

1. Anderson GF. Chronic care: making the case for ongoing care: Robert Wood Johnson Foundation; 2010.
2. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *The Lancet*. 2012; 380(9836):37–43.
3. Buttorff C, Ruder T, Bauman M. Multiple chronic conditions in the United States. Santa Monica (CA): RAND Corporation. 2017.
4. Wolff JL, Starfield B, Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. *Archives of internal medicine*. 2002; 162(20):2269–76. <https://doi.org/10.1001/archinte.162.20.2269> PMID: 12418941
5. United Nations DoE Social Affairs PD. World Population Ageing 2015 (ST/ESA/SER. A/390). United Nations New York, NY; 2015.

6. Kingston A, Robinson L, Booth H, Knapp M, Jagger C, project M. Projections of multi-morbidity in the older population in England to 2035: estimates from the Population Ageing and Care Simulation (PACSim) model. *Age and ageing*. 2018; 47(3):374–80. <https://doi.org/10.1093/ageing/afx201> PMID: 29370339
7. Marengoni A, Angleman S, Melis R, Mangialasche F, Karp A, Garmen A, et al. Aging with multimorbidity: a systematic review of the literature. *Ageing research reviews*. 2011; 10(4):430–9. <https://doi.org/10.1016/j.arr.2011.03.003> PMID: 21402176
8. Vogeli C, Shields AE, Lee TA, Gibson TB, Marder WD, Weiss KB, et al. Multiple chronic conditions: prevalence, health consequences, and implications for quality, care management, and costs. *Journal of general internal medicine*. 2007; 22(3):391–5.
9. Salive ME. Multimorbidity in older adults. *Epidemiologic reviews*. 2013; 35(1):75–83. <https://doi.org/10.1093/epirev/mxs009> PMID: 23372025
10. Gerteis J, Izrael D, Deitz D, LeRoy L, Ricciardi R, Miller T, et al. Multiple chronic conditions chartbook. Rockville, MD: Agency for Healthcare Research and Quality. 2014.
11. Nunes BP, Flores TR, Mielke GI, Thume E, Facchini LA. Multimorbidity and mortality in older adults: a systematic review and meta-analysis. *Archives of gerontology and geriatrics*. 2016; 67:130–8. <https://doi.org/10.1016/j.archger.2016.07.008> PMID: 27500661
12. Marengoni A, Von Strauss E, Rizzuto D, Winblad B, Fratiglioni L. The impact of chronic multimorbidity and disability on functional decline and survival in elderly persons. A community-based, longitudinal study. *Journal of internal medicine*. 2009; 265(2):288–95. <https://doi.org/10.1111/j.1365-2796.2008.02017.x> PMID: 19192038
13. Landi F, Liperoti R, Russo A, Capoluongo E, Barillaro C, Pahor M, et al. Disability, more than multimorbidity, was predictive of mortality among older persons aged 80 years and older. *Journal of clinical epidemiology*. 2010; 63(7):752–9. <https://doi.org/10.1016/j.jclinepi.2009.09.007> PMID: 20056387
14. Menotti A, Mulder I, Nissinen A, Giampaoli S, Feskens EJ, Kromhout D. Prevalence of morbidity and multimorbidity in elderly male populations and their impact on 10-year all-cause mortality: The FINE study (Finland, Italy, Netherlands, Elderly). *Journal of clinical epidemiology*. 2001; 54(7):680–6. [https://doi.org/10.1016/s0895-4356\(00\)00368-1](https://doi.org/10.1016/s0895-4356(00)00368-1) PMID: 11438408
15. Wang C, Baldwin L-M, Saver BG, Dobie SA, Green PK, Cai Y, et al. The contribution of longitudinal comorbidity measurements to survival analysis. *Medical care*. 2009; 47(7):813. <https://doi.org/10.1097/MLR.0b013e318197929c> PMID: 19536031
16. St John PD, Tyas SL, Menec V, Tate R. Multimorbidity, disability, and mortality in community-dwelling older adults. *Canadian Family Physician*. 2014; 60(5):e272–e80. PMID: 24829022
17. Woo J, Leung J. Multi-morbidity, dependency, and frailty singly or in combination have different impact on health outcomes. *Age*. 2014; 36(2):923–31. <https://doi.org/10.1007/s11357-013-9590-3> PMID: 24091565
18. Collins LM, Lanza ST. Latent class and latent transition analysis: With applications in the social, behavioral, and health sciences: John Wiley & Sons; 2010.
19. Larsen FB, Pedersen MH, Friis K, Glümer C, Lasgaard M. A latent class analysis of multimorbidity and the relationship to socio-demographic factors and health-related quality of life. A National Population-Based Study of 162,283 Danish adults. *PloS one*. 2017; 12(1):e0169426. <https://doi.org/10.1371/journal.pone.0169426> PMID: 28056050
20. Zheng DD, McCollister K, Christ S, Lam BL, Feaster DJ, Lee DJ. Chronic condition patterns in the US population and their association with health related quality of life. *Preventive Medicine*. 2020:106102. <https://doi.org/10.1016/j.ypmed.2020.106102> PMID: 32360766
21. Olaya B, Moneta MV, Caballero FF, Tyrovolas S, Bayes I, Ayuso-Mateos JL, et al. Latent class analysis of multimorbidity patterns and associated outcomes in Spanish older adults: a prospective cohort study. *BMC geriatrics*. 2017; 17(1):186. <https://doi.org/10.1186/s12877-017-0586-1> PMID: 28821233
22. Whitson HE, Johnson KS, Sloane R, Cigolle CT, Pieper CF, Landerman L, et al. Identifying patterns of multimorbidity in older Americans: application of latent class analysis. *Journal of the American Geriatrics Society*. 2016; 64(8):1668–73. <https://doi.org/10.1111/jgs.14201> PMID: 27309908
23. Park B, Lee HA, Park H. Use of latent class analysis to identify multimorbidity patterns and associated factors in Korean adults aged 50 years and older. *PloS one*. 2019; 14(11). <https://doi.org/10.1371/journal.pone.0216259> PMID: 31721778
24. Li Y, Ragland M, Austin E, Young K, Pratte K, Hokanson JE, et al. Co-Morbidity Patterns Identified Using Latent Class Analysis of Medications Predict All-Cause Mortality Independent of Other Known Risk Factors: The COPDGene® Study. *Clinical Epidemiology*. 2020; 12:1171. <https://doi.org/10.2147/CLEP.S279075> PMID: 33149694
25. National Center for Health Statistics. NCHS Data Linked to NDI Mortality Files: Centers for Disease Control and Prevention; 2019 [<https://www.cdc.gov/nchs/data-linkage/mortality.htm>].

26. National Center for Health Statistics. National Health Interview Survey. Questionnaires, Datasets, and Related Documentation 2017 [[https://www.cdc.gov/nchs/nhis/nhis\\_questionnaires.htm](https://www.cdc.gov/nchs/nhis/nhis_questionnaires.htm)].
27. Parsons VL, Moriarity CL, Jonas K, Moore TF, Davis KE, Tompkins L. Design and estimation for the national health interview survey, 2006–2015. 2014.
28. Botman SL, Jack SS. Combining national health interview survey datasets: issues and approaches. *Statistics in medicine*. 1995; 14(5-7):669–77. <https://doi.org/10.1002/sim.4780140523> PMID: 7792456
29. Goodman RA, Posner SF, Huang ES, Parekh AK, Koh HK. Defining and measuring chronic conditions: Imperatives for research, policy, program, and practice. *Preventing Chronic Disease*. 2013; 10.
30. Office of the Assistant Secretary for Health. U.S. Department of Health & Human Services Initiative on Multiple Chronic Conditions: U.S. Department of Health & Human Services; 2015 [<https://www.hhs.gov/ash/about-ash/multiple-chronic-conditions/index.html>].
31. Bernstein AB, Rensburg RE. Estimated prevalence of people with cognitive impairment: results from nationally representative community and institutional surveys. *The Gerontologist*. 2007; 47(3):350–4. <https://doi.org/10.1093/geront/47.3.350> PMID: 17565098
32. Luo H, Yu G, Wu B. Self-reported cognitive impairment across racial/ethnic groups in the United States, National Health Interview Survey, 1997–2015. *Preventing chronic disease*. 2018; 15:E06–E.
33. Kessler RC, Barker PR, Colpe LJ, Epstein JF, Gfroerer JC, Hiripi E, et al. Screening for serious mental illness in the general population. *Archives of general psychiatry*. 2003; 60(2):184–9. <https://doi.org/10.1001/archpsyc.60.2.184> PMID: 12578436
34. Christ SL, Lee DJ, Fleming LE, LeBlanc WG, Arheart KL, Chung-Bridges K, et al. Employment and occupation effects on depressive symptoms in older Americans: does working past age 65 protect against depression? *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*. 2007; 62(6):S399–S403. <https://doi.org/10.1093/geronb/62.6.s399> PMID: 18079428
35. Kessler RC, Andrews G, Colpe LJ, Hiripi E, Mroczek DK, Normand S-L, et al. Short screening scales to monitor population prevalences and trends in non-specific psychological distress. *Psychological medicine*. 2002; 32(6):959–76. <https://doi.org/10.1017/s0033291702006074> PMID: 12214795
36. Weissman J, Pratt LA, Miller EA, Parker JD. Serious Psychological Distress Among Adults, United States, 2009–2013: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics; 2015.
37. National Center for Health Statistics. Public-use Linked Mortality File: Office of Analysis and Epidemiology, Hyattsville, Maryland; 2019 [NHIS linked with NDI, mortality follow up through Dec. 31, 2015]. <https://www.cdc.gov/nchs/data-linkage/mortality-public.htm>.
38. Nagin DS, NAGIN D. Group-based modeling of development: Harvard University Press; 2005.
39. Asparouhov T, Muthén B. Residual associations in latent class and latent transition analysis. *Structural Equation Modeling: A Multidisciplinary Journal*. 2015; 22(2):169–77.
40. Asparouhov T, Muthén B. Auxiliary variables in mixture modeling: Three-step approaches using M plus. *Structural Equation Modeling: A Multidisciplinary Journal*. 2014; 21(3):329–41.
41. Bassuk SS, Wypij D, Berkman LF. Cognitive impairment and mortality in the community-dwelling elderly. *American journal of epidemiology*. 2000; 151(7):676–88. <https://doi.org/10.1093/oxfordjournals.aje.a010262> PMID: 10752795
42. Dewey ME, Saz P. Dementia, cognitive impairment and mortality in persons aged 65 and over living in the community: a systematic review of the literature. *International journal of geriatric psychiatry*. 2001; 16(8):751–61. <https://doi.org/10.1002/gps.397> PMID: 11536341
43. Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and meta-regression analysis. *Archives of general psychiatry*. 2006; 63(5):530–8. <https://doi.org/10.1001/archpsyc.63.5.530> PMID: 16651510
44. Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR, Ofstedal MB, et al. Prevalence of cognitive impairment without dementia in the United States. *Annals of internal medicine*. 2008; 148(6):427–34. <https://doi.org/10.7326/0003-4819-148-6-200803180-00005> PMID: 18347351
45. Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J, DeKosky S. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. *Jama*. 2002; 288(12):1475–83. <https://doi.org/10.1001/jama.288.12.1475> PMID: 12243634
46. Gilman SE, Sucha E, Kingsbury M, Horton NJ, Murphy JM, Colman I. Depression and mortality in a longitudinal study: 1952–2011. *Cmaj*. 2017; 189(42):E1304–E10. <https://doi.org/10.1503/cmaj.170125> PMID: 29061855
47. Boyle PA, Yu L, Wilson RS, Gamble K, Buchman AS, Bennett DA. Poor decision making is a consequence of cognitive decline among older persons without Alzheimer's disease or mild cognitive impairment. *PloS one*. 2012; 7(8):e43647. <https://doi.org/10.1371/journal.pone.0043647> PMID: 22916287



48. Zheng DD, Christ SL, Lam BL, Feaster DJ, McCollister K, Lee DJ. Patterns of Chronic Conditions and Their Association With Visual Impairment and Health Care Use. *JAMA ophthalmology*. 2020. <https://doi.org/10.1001/jamaophthalmol.2020.0052> PMID: [32105300](https://pubmed.ncbi.nlm.nih.gov/32105300/)
49. Ahmadi S-F, Streja E, Zahmatkesh G, Streja D, Kashyap M, Moradi H, et al. Reverse epidemiology of traditional cardiovascular risk factors in the geriatric population. *Journal of the American Medical Directors Association*. 2015; 16(11):933–9. <https://doi.org/10.1016/j.jamda.2015.07.014> PMID: [26363864](https://pubmed.ncbi.nlm.nih.gov/26363864/)