

Multimorbidity and Mortality: A Review of U.S. Evidence and Modelling Approaches

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Abstract: Multimorbidity, or the presence of two or more chronic conditions, represents a significant and expanding public health concern in the U.S., particularly among older adults and underserved subpopulations. This article combines results of various US longitudinal and cross-sectional studies on the association of multimorbidity and mortality with a focus on modeling strategies as well as public health implications. It was demonstrated that the presence of multi-morbidity is associated with an increased mortality risk in a dose-response-like fashion, as shown by steadily increasing hazard ratios. Combinations like cardiometabolic and mental health disorders have disproportionately high mortality burdens. Race, poverty, and access to healthcare are the key effect modifiers with significant race and rural disparities in results. Typical modeling methods include Cox Proportional Hazards models, competing risks models, latent class analysis, the more sophisticated survival tree methods, a wrapper of deep learning, and recurrent neural networks. However, interpretation and prediction strengths differ between these models, and unification of comorbidity definitions, lack of representation of minority groups, and longitudinal cohort-based causal modeling are some persistent challenges. Real-world data integration and generalizability gaps also hinder policy translation. We emphasize advanced modeling methods, diverse and representative cohorts, and integrating electronic health records with administrative databases to overcome the limitations inherent to forecasting. Dealing with multimorbidity is an action at the national level; in addition to being implemented, correct modeling has a great potential for defining health care policy for Medicare, preventing diseases, and even distributing resources more equitably.

Keywords: Multimorbidity, Mortality, Chronic Disease, Predictive Modeling, Public Health.

INTRODUCTION

There is limited consensus in the published literature on what constitutes multimorbidity; however, it is regularly defined as an individual having 2 or more long-term health conditions (comorbidities), with no single condition being considered primary. (World Health Organization, 2016). These were a spectrum of physical non-communicable diseases, mental health conditions, and long-term infectious diseases that may be comorbid with and/or causally related to OSA. What distinguishes this notion from comorbidity (in which one condition is considered the index disease and others are ancillaries) is that it pointedly codifies conditions mostly due to a disorder of a single organ or system. This has become a growing problem in the USA due to an aging society and the consequent increase in chronic diseases, such as hypertension, diabetes, and chronic respiratory disease (Zhu *et al.*, 2020).

Multimorbidity is one of the greatest challenges for modern healthcare systems globally. Related to higher mortality, decreased quality of life, increased healthcare costs, and complex clinical management. Compared to patients with only one disease, patients with multimorbidity require more complex care and are prone to faster functional decline, hospitalizations for conditions exacerbated by non-adherence or drug-drug interactions, and events related to inappropriate medications. Dealing with multimorbidity requires a move away from the standard of care addressing disease by

disease, focusing on coordination, prevention, and care goal setting (Caraballo *et al.*, 2022).

Among the U.S. adult population, there are some 32.9% with two or more chronic conditions; 20.7% have three or more (Cezard *et al.*, 2021). Age-standardized prevalence increases exponentially with age, where it eventually became as high as 73% in the age group 65years and older (32.9% and 73.0%, respectively). Furthermore, national trends from 1999 to 2018 indicate that multimorbidity, especially having five or more non-communicable diseases, is rising fastest among middle-aged and older adults and is associated with substantially increased risks of overall mortality, particularly in younger adults with ≥ 5 NCDs (Caraballo *et al.*, 2022).

Multimorbidity is highly associated with increased risk of mortality and escalating healthcare costs. Compared to adults with single or no chronic conditions, those with multiple chronic conditions are at significantly greater risk of mortality (Kazuaki *et al.*, 2016). Then, there may be a compounding effect as disease clusters like diabetes, coupled together with cardiovascular conditions, all but automatically mean that the greater the number of such occurrences, the higher the hazard ratio. Consequently, average direct medical costs increase accordingly: per-person spending jumps from about \$4,176 for those with at least one chronic illness to over \$10,800 for those with four or more conditions (attributable

both to greater utilization and poorer health status, like reporting “fair/poor perceived health”) (Kazuaki *et al.*, 2016). Multimorbidity is a massive driver of U.S. healthcare spending, as chronic conditions comprise more than 75% of duty expressed in annual health expenditures in the country, and combinations such as diabetes plus cardiovascular disease or mental health conditions can run \$37,000 to \$85,000 per person each year (yes: tens of thousands annually) (Kazuaki *et al.*, 2016).

This review considers mainly U.S.-based evidence regarding empirical epidemiology of multimorbidity, relationships between multimorbidity and mortality in the United States literature, and the modelling approaches used to predict mortality risk from multimorbidity based on U. S cohort data, including Medicare cohorts, NHANES cohort data, BRFSS adults surveys mechanisms, and health system cohorts. We intentionally exclude such international studies other than in an illustrative context, so that findings and implications are directly relevant to US health policy and clinical practice (Schiltz, 2022). This paper has set the primary aims to review the available evidence about multimorbidity prevalence and its lethality in the U.S., and to present and evaluate a variety of prediction modeling methods that extend from common linear models (such as Cox regression, Charlson Comorbidity Index) towards advanced machine learning techniques for anticipating multimorbidity-associated mortality (Schiltz, 2022). Our objective is to review methodologically strong studies, to report performance characteristics of the models, questioning accuracy and fit, and to attempt to derive lessons for both further research and healthcare policy-making in U.S. health systems (Caraballo *et al.*, 2022).

Epidemiology of Multimorbidity in the United States

Multi-morbidity, defined as having two or more chronic conditions, is a common feature in the United States; based on 2013–2014 NHANES data, 59.6 % of adults ≥ 20 years had two or more chronic conditions; 38.5 % had three or more, and 22.7% four or more (Rocca *et al.*, 2014). Prevalence rises significantly with age, 91.8% of those ≥ 65 with ≥ 2 conditions vs 70.6% for ages 45–64, and 37.5% for ages 20–44 [Dana *et al.*, 2018;]. In a second large study, prevalence increased from 7.9 to 73.0% for >2 conditions (ages 18–39 to ages 65+) and had similar gradients for >3 and >4 conditions (Schiltz, 2022). Among

both, the women's prevalence was slightly higher: NHANES 2013–2014 data showed female prevalence of ≥ 2 multimorbidities at 58.4% versus 55.9% in men ($p = 01$). Temporal trends illustrate that the burden of multiple conditions carried by women is greater at any age. These disparities are even more pronounced when broken down by race and ethnicity. Results from NHANES 2013–14 show non-Hispanic Whites and non-Hispanic Blacks with a higher age-standardized prevalence (61.2% and 57.4%, respectively) than Hispanic patients (52.0%) or Asian patients (41.3%) (Mossadeghi *et al.*, 2023; Dana *et al.*, 2018). In another survey (NHIS 1999–2018), multimorbidity prevalence was estimated to be 17.4% among Black participants in 1999, compared with 10.7% for Hispanic, 13.5% for White and 5.9% for Asian participants; these shares increased over time for all groups by the subsequent decade of late results up to at latest two-decade lapsed data from NHIS through (Caraballo *et al.*, 2022) but the gap persisted: Black participants once again exceeded White participation by \sim a clinically significant amount of about one percent of absolute proportion points. Cardiometabolic multimorbidity (hypertension + diabetes \pm coronary disease): 14.4% in 2017–2018, was more common among older adults, males, and non-Hispanic Blacks (Cheng *et al.*, 2022). Socioeconomic disadvantage was also associated with multimorbidity. Among adults aged 30–64 from NHIS (2002–2014), having less than a high school education (vs bachelor's degree) was associated with greater odds of multimorbidity: OR=1.58; 95% CI = 1.50, 1.66, and the risk was progressively lower for high school or some college graduates: OR=1.32; 95% CI = 1.27, 1.37; odds were slightly higher among non-Hispanic Black versus White individuals: OR=1.07; 95% CI = 1.02, 1.11 Caraballo *et al.*, 2022). For social determinants, including health insurance and a usual source of care, were independently associated with ≥ 2 chronic conditions (King *et al.*, 2018), whereas income and education had weaker direct associations in cross-sectional NHANES 2017–2018 analysis.

Vulnerable Populations

Almost all individuals aged 65 and older have multimorbidity, with prevalence rates exceeding 90% (Kazuaki *et al.*, 2016). There were also persistent racial disparities, with the non-Hispanic Black American population consistently enjoying higher levels of multimorbidity than their white counterparts, again with little change in these rates between 1999 and 2018 (Caraballo *et al.*, 2022;

Mossadeghi *et al.*, 2023). The risk is also significantly increased among the working-aged adults, mainly due to socioeconomic factors (Vicki *et al.*, 2017; Mossadeghi *et al.*, 2023). Lower levels of education, together with a lack of health insurance or regular access to healthcare, are critical determinants. There is an increasing

multimorbidity burden among aging as well as middle-aged adults, particularly prominent among individuals residing in the most deprived communities based on the individual-level Social Deprivation Index and served by community health centers (Valenzuela *et al.*, 2024).

Table 1: Key Patterns

Demographic Group	Multimorbidity (≥ 2 Conditions) Prevalence
Adults (≥ 20 y), NHANES 2013–14	~59.6%
Age 65+	~91.8%
Females vs Males	58.4% vs 55.9%
Non-Hispanic White	~61.2%
Non-Hispanic Black	~57.4%
Hispanic	~52.0%
Asian	~41.3%
Low education ($< HS$)	OR = 1.58 vs \geq bachelor's
Socially deprived communities	Higher burden across all age strata

MULTIMORBIDITY AND MORTALITY: EVIDENCE FROM U.S. STUDIES

Data from studies in the US repeatedly demonstrate a steep dose–response association between multimorbidity status and mortality risk, and for up to twenty years (self-report and measured data from NHANES-retrospective cohort of 1999–2018; $n \approx 38,977$) adults suffering with five or more NCDs were at ~4.5-times higher risk for all-cause death compared to those without any NCD, wherein important interactions were also evident by age, race/ethnicity and education (Sun *et al.*, 2023). Southern Community Cohort Study (SCCS) longitudinal data suggested a collective increment in mortality hazard with added cardiometabolic comorbidities: all-cause and cardiovascular mortal hazards approximately were 3.81 and 6.18 for individuals with four conditions; significant reductions in life expectancy based on years lost (median of 16 lost due to such comorbidities by mid-40s); and more substantial effects among Black compared to White study participants (Pradhan *et al.*, 2024). The Jackson Heart Study also found high rates of mortality among African Americans reporting both diabetes and stroke or diabetes and coronary heart disease, with mortality rates at up to 84 deaths per 1,000 person-years and hazard ratios over 2.2 for some combinations (Joseph *et al.*, 2022). Cross-sectional analyses, for example, by the CDC in their NHANES 2017–2018 study, revealed recorded multimorbidity to be lower among populations with poor access to care; a likely reflection of underdiagnosis rather than lower risk, and thereby in part serving as a testament to the influence of social determinants (Mossadeghi *et*

al., 2023). There are complex relationships between age and risk, with relative mortality being higher for high multimorbidity counts among working-age adults (although the absolute mortality burdens were substantially larger in older people (Jani *et al.*, 2019). Second, race and socioeconomic status are critical as linkages between multimorbidity mortality associations through education were diverse by racial/ethnic group (Sun *et al.*, 2023; Pradhan *et al.*, 2024), with Black persons being vulnerable to higher mortality risks than other groups. According to Fan *et al* (2022), different conditions had lung clusters with varied mortality hazards; the cardiometabolic clusters were at the highest HRs >2 and 4, unlike other disease groupings (Joseph *et al.*, 2022). These increasing trends in multimorbidity prevalence by hospitalization from 1993 to 2012 were observed across all racial/ethnic groups, as well as among Black patients, and the highest growth in conditions such as hypertension, renal failure, and heart failure highlights a broadening of population-level mortality risk over time (Mohamud *et al.*, 2023).

Modeling Approaches for Multimorbidity and Mortality

U.S.-Based Models of Multimorbidity and Mortality research has employed a wide variety of traditional and emerging methods to model multimorbidity and mortality. Multivariable Cox proportional hazards models are employed most frequently; in larger retrospective cohorts such as NHANES 1999–2018, these models link multimorbidity counts to graded hazard ratios for all-cause mortality of approximately 1.5 for one

condition, 2.4 for two to four conditions, and 4.5 for five or more following adjustment for demographic and socioeconomic covariates, with notable interactions evident by age as well as race/ethnicity therein and education status (Nazar *et al.*, 2023; Sun *et al.*, 2023). Interpretable (yet black-box), interpretable, and often effective for time-to-event data as long as the proportional hazards assumption holds, but also requiring manual specification of nonlinearities. Although less frequently used, competing risks models are useful in multimorbidity studies where cause-specific mortality events (e.g., cardiovascular vs cancer deaths) may compete, but have the caveats that they can be difficult to interpret and require sufficient numbers of events for each cause. For example, latent class analysis has been used in large U.S. cohorts such as NHIS/NHID to classify multimorbidity patterns into clinically-relevant groups (e.g., “healthy,” “respiratory,” “complex

cardiometabolic”) with distinct mortality risks (Zheng *et al.*, 2021; Zhu *et al.*, 2020), but there are subjective decisions on the number of classes and risk of misclassification. In the U.S.-focused multimorbidity literature, we identified fewer studies using tree-based methods, such as survival trees and random survival forests, which can automatically model nonlinearities and interactions without making proportional hazards assumptions (Zhu *et al.*, 2020). State-of-the-art deep learning methods like DeepSurv and various LSTM-based frameworks, although nascent in multimorbidity epidemiology as a whole, have shown promise in capturing non-linear temporal relationships of structured EHR data for survival (time-to-event) prediction at the individual level with time-dependent covariate adjustments serving U.S. EHR-based cohorts, yet being somewhat opaque to clinical interpretation and data-intensive in nature with model hyper-parameter tuning complexities.

Table 2: Summary Comparison of Models

Model Type	Strengths	Limitations	U.S. Multimorbidity Applicability
Cox PH	Interpretable HRs, handles censoring, common	Assumes proportional hazards, limited nonlinearity	Used widely with NHANES / NHIS data
Competing Risks	Distinguishes cause-specific endpoints	Complexity requires enough cause-specific events	Relevant when multimorbidity poses differential causes
Latent Class Analysis	Reveals clustered phenotypes, probabilistic	Class choice is subjective, and misclassification bias	Used to define clusters and examine mortality differences
Survival Trees / RSF	Handles nonlinearities, high-dimensional data	Less interpretable, tuning needed	Emerging for EHR-based mortality modeling
Deep Learning (RNN/NN)	Captures temporality and complex interactions	Data-demanding, opaque model structure	Promising for large EHR-linked U.S. datasets

PRACTICAL INSIGHTS

Cox models have traditionally served as a cornerstone for risk of death assessment by counting the number of comorbidities in large national cohorts as Cox models are useful and interpretable, making them robust; however, latent class analysis (LCA) has the potential to enhance our understanding by providing different phenotypes of multimorbidity beyond simple counts that relate with differing mortality. Simple Cox-proportional hazards regression models with LCA cluster membership are easily interpretable; however, they will not handle complex interactions and rich, temporally granular datasets as can be attributed to tree-based and deep learning approaches. Integration of these models in the same training-test set seems an appealing option consistent with Gene for lattice work. Nevertheless, there remain important obstacles to research in this area that are directly attributable to the absence of a single definition of

multimorbidity that has achieved universal acceptance (Plana-Ripoll *et al.*, 2024). Counts, weighted indices such as the Charlson Index or Elix Hauser Count, and indices incorporating function and syndromes vary between surveys; thus, comparability is thwarted. The hyperbolic treatment of multimorbidity may also lead to a misunderstanding of the effect on other pathologies, duration, onset-time, and/or somatopsychic studies (Fernandes-Nino *et al.*, 2016). Observational designs are subject to misclassification, confounding by indication, measurement error, and linkage bias, particularly when treatment selection is affected by multimorbidity. Unless modeled correctly, many EHR-based predictive models that use a longitudinal cohort suffer from inference of sicker patients visiting more frequently, which leads to informative observation bias. The prevalence of cross-sectional designs restricts information on disease accumulation over time, and actual

longitudinal U.S. research is less common than in Europe, with various inconsistent trajectory modeling strategies that have been unable to reach a consensus best practice (Cezard *et al.*, 2021). Sampling bias towards higher-SES, healthier populations and underpowered ethnic minority subgroup analyses; Exclusion of multimorbid individuals from clinical trials, up to 91% of trial participants compared to community samples do not have multimorbidity (Xu *et al.*, 2017; Hanlon *et al.*, 2019). They do not model intersectional impacts of race, gender, and economic deprivation. Although U.S. EHR and administrative datasets could potentially facilitate predictive and causal modeling, many studies continue to rely on less granular survey data, and few employ causal inference methods, including mediation analysis, instrumental variables, marginal structural models, or target trial emulations, which would increase relevance for policy decisions (Cezard *et al.*, 2021). There are missingness and non-constant observation times to model together with an outcome; not accounting for them induces bias in real-world data. These problems of conceptual fragmentation, time depths, biased sampling, and poor explanatory power still limit the comparability, policy relevance, and equity impact of multimorbidity research.

POLICY AND PUBLIC HEALTH IMPLICATIONS

Multimorbidity is a major driver of healthcare expenditure in the United States, accounting for over 90% of Medicare spending despite affecting a minority of enrollees, with costs rising non-linearly as additional conditions accumulate due to polypharmacy, specialist consultations, hospitalizations, and complex care coordination. Individuals with four or more chronic conditions incur over \$20,000 annually, more than quadruple the costs for those with one or none, while also facing higher rates of preventable emergency visits and hospitalizations that add to avoidable system strain. The U.S. healthcare system, designed largely for single-disease management, struggles with fragmented care that leads to redundant or conflicting treatments, adverse drug interactions, patient confusion, nonadherence, and increased provider burnout, ultimately lowering care quality and increasing diagnostic errors. Multimorbidity disproportionately affects racial and ethnic minorities, low-income and low-education groups, and rural communities, emerging earlier and more severely in these populations due to social determinants such as housing instability, food

insecurity, environmental exposures, and limited access to care. For example, Black Americans develop multimorbidity nearly a decade earlier than White Americans, while Indigenous populations carry a higher but often undercounted burden. Predictive modeling offers a powerful tool for policy and prevention, enabling Medicare and Medicaid to identify high-risk individuals before costly complications occur, inform integrated care programs, and guide population-level forecasting for budgeting and resource allocation. By modeling multimorbidity trajectories, these approaches can shape tailored screening guidelines, precision public health interventions, and behavioral nudges, while in value-based payment systems, they support accurate risk adjustment, population health monitoring, and the integration of social determinants into patient risk profiles to align prevention, equity, and system sustainability.

Multimorbidity poses a complex, systemic challenge with profound implications for U.S. healthcare financing, delivery, and equity. Its rising prevalence threatens the sustainability of programs like Medicare and Medicaid. However, leveraging advanced predictive modeling offers a path forward, enabling smarter allocation of resources, targeted prevention, and more personalized, equitable care. Future policy must be grounded in both population-level data and individual-level forecasting, with a strong focus on reducing disparities and enhancing system responsiveness to multimorbidity's evolving burden.

Recommendations for Future Research

Despite advances in understanding the relationship between multimorbidity and mortality, research remains limited by methodological and representational gaps, underscoring the need for more sophisticated and inclusive approaches. Future studies should move beyond reliance on traditional models like Cox proportional hazards by adopting advanced and interpretable techniques such as deep learning models to capture time-varying risks and nonlinear interactions, survival ensemble methods and explainable machine learning to balance predictive accuracy with interpretability, and joint modeling of longitudinal risk factors with survival data to identify the most lethal combinations and sequences of conditions for early intervention and personalized care. Efforts must also focus on building more diverse and representative cohorts by oversampling racial/ethnic minorities, low-income groups, and

rural populations, conducting intersectional analyses by age, gender, and disability status, and engaging communities to ensure cultural relevance and data quality, thereby preventing predictive models from perpetuating inequities. Strengthening causal inference through methods like marginal structural models, g-computation, and natural experiments, as well as establishing prospective longitudinal cohorts with consistent follow-up, will be vital for uncovering disease trajectories and mortality tipping points. Additionally, integrating electronic health records with claims data, mortality records, and social determinants, supported by federated learning frameworks and a national data infrastructure akin to the UK Biobank or All of Us but tailored for the U.S., would overcome data fragmentation and enable population-wide insights while preserving individual-level detail.

CONCLUSION

Multimorbidity is far from a new challenge for the United States' health landscape particularly in aging and socioeconomically vulnerable subpopulations. These findings are linked to an elevated mortality risk, increased healthcare utilization, and reduced quality of life, warranting national policy consideration and collaborative public health action. There is a growing evidence base, but existing models to understand and reduce multimorbidity-related mortality are constrained by outdated modeling approaches, a lack of generalizability to diverse populations, and fragmented data systems. Their continual use of cross-sectional or descriptive analytics has been limiting actionability insights, and a lack of comprehensive longitudinal modeling disables fair design for intervention.

It will require a deliberate movement to both data-driven and causal, but also an inclusivity moving this field forward. With novel statistical and machine learning models, and in conjunction with broader cohorts of more generalizable data sources, their work has the potential to better predict risk, uncover key disease pathways, and inform early interventions. These modeling frameworks are essential in informing Medicare planning, distributing hospital resources, and population health strategies to mitigate preventable deaths. A national imperative addressing multimorbidity. Finally, linking methodological innovation and public health action offers a critical opening for reducing mortality inequalities and increasing life expectancy at a national level in the

United States. With an aging U.S. population and increasingly complex disease profiles, the demand for data-based, anticipatory, and just solutions has never been higher.

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