Annals of Epidemiology 37 (2019) 24–30

Contents lists available at ScienceDirect

Annals of Epidemiology

Original article

Personalized and typical concurrent risk of limitations in social activity and mobility in older persons with multiple chronic conditions and polypharmacy

Terrence E. Murphy, PhD [a, b], Gail J. McAvay, PhD [a], George O. Agogo, PhD [a], Heather G. Allore, PhD [a, b, *]

[a] Department of Internal Medicine, Section of Geriatrics, Yale School of Medicine, New Haven, CT
[b] Department of Biostatistics, Yale School of Public Health, New Haven, CT

ARTICLE INFO

Article history:
Received 26 March 2019
Accepted 5 August 2019
Available online 9 August 2019

Keywords:
Longitudinal analysis
Joint modeling
Inverse probability of treatment weighting
Personalized concurrent risk
Typical concurrent risk

ABSTRACT

Purpose: We define personalized concurrent risk (PCR) as the subject-specific probability of an index outcome within a defined interval of time, while currently at risk for a separate outcome, where the outcomes are not mutually exclusive and can be jointly modeled with a shared random intercept. We further define typical concurrent risk as the risk obtained by setting the random intercept to null.
Methods: Drawing data from the Medical Expenditure Panel Survey (cohorts 2008–2013), we jointly model limitations in social activity and mobility over two years among older community-dwelling persons with both hypertension and chronic obstructive pulmonary disease. The joint model uses inverse probability of treatment weighting based on each participant's baseline propensity of polypharmacy (≥5 classes of medication).
Results: Even among participants with the same covariates, older persons with multiple chronic conditions exhibit wide-ranging heterogeneity of the treatment effect from polypharmacy, a risk factor for negative health outcomes among older persons. The magnitude of the PCRs is dominated by the value of the subject-specific random effect.
Conclusions: Estimates of PCR and typical concurrent risk can be calculated from national or institutional data sets and may facilitate the practice of personalized care for older patients with multiple chronic conditions.

© 2019 Elsevier Inc. All rights reserved.

A growing proportion of the U.S. population has multiple chronic conditions (MCCs). Approximately 75% of adults older than 65 years are affected by two or more chronic medical conditions [1]. As the prevalence of older adults with chronic conditions increases, so do health care utilization, treatment burden, and the frequency of adverse drug events. Considering MCC's sizable impact on the aging U.S. population, the Department of Health and Human Services published “Multiple Chronic Conditions: A Strategic Framework” [2] and outlined strategies including analytic methods. However, the goal of health care, namely “the maximization of benefit and minimization of harm,” has largely focused on single diseases. It is not uncommon for older persons to take between 5 and 10 medications for a comparable number of chronic conditions. Yet, methods that examine how multiple medications affect patient-centered and correlated outcomes are rarely applied. Clinicians, policy makers, and investigators have called for innovative and feasible methods for enhancing shared clinical decision-making with patients who endure MCCs [3–6]. We posit that a better understanding of how patient characteristics, both observed and unobserved, contribute to widespread heterogeneity of treatment effect (HTE) is of particular importance when modeling patient-centered outcomes.

A large survey of older patients ($n = 4277$) that examined their priorities for on-going medical care listed their top two as effective reduction of symptoms and maintenance of physical function, respectively [7]. This underscores the need to better understand how factors affect the probability of patient-centered outcomes, such as limitations in social activity and mobility, which are simultaneously correlated and nonmutually exclusive. Knowing the probability of experiencing pairs of patient-centered outcomes

All coauthors state having no conflicts of interest with regard to the contents of this manuscript.

* Corresponding author. Yale University School of Medicine, 300 George St, Suite 775, New Haven, CT 06511. Tel.: +1(203) 737-1892; fax: (203) 785-4823.
E-mail address: heather.allore@yale.edu (H.G. Allore).

https://doi.org/10.1016/j.annepidem.2019.08.001
1047-2797/© 2019 Elsevier Inc. All rights reserved.

within the next year may help patients and providers better achieve goals of care [8]. Jointly modeling outcomes with a shared random intercept provides a means of harnessing the longitudinal correlation of two outcomes that can occur and reoccur without precluding the other, that is, concurrent outcomes [9].

In this article, we jointly model the concurrent outcomes of limitations in social activity and mobility among older community-dwelling persons with both hypertension and chronic obstructive pulmonary disease (COPD) in the Medical Expenditure Panel Survey (MEPS), a nationally representative prospective survey of adults in the United States. The motivation for using the MEPS cohort is that many persons with this pairing of MCCs take multiple medications to control their underlying diseases [10]. Our primary exposure is polypharmacy (concomitant use of $\geq$ five medication classes), which in older adults [11] has been associated with negative outcomes such as reduced mobility, quality of life, injurious falls, hospitalization, and mortality [12–15]. Over 60% of older adults treated for hypertension take two or more classes of antihypertensive medications and persons with COPD commonly take dual or triple therapy to control their progressive disease [10]. Notwithstanding the high likelihood of polypharmacy among persons with hypertension and COPD, Boyd et al showed that there were no guidelines for treatment of multimorbid older adults with either hypertension or COPD [16]. Our objective is to demonstrate how joint modeling of limitations in social activity and mobility over two years of follow-up among older adults with hypertension and COPD allows the calculation of their personalized concurrent risks (PCRs). In these calculations, inverse probability of treatment weights (IPTWs) is used to address confounding of baseline characteristics with the exposure of polypharmacy. We further demonstrate that for persons with a given set of covariate values, the fixed effect coefficients from the joint model allow the calculation of their typical concurrent risk (TCR) for each outcome. We posit that absolute measures, such as the probability of an outcome based on personal characteristics, can be much more informative than the measures of relative risk typically presented in epidemiological studies [17, 18].

Methods

Study population

The study included participants in the MEPS panels from 2008 to 2013, who were followed over 2.5 years, with interviews conducted approximately every 6 months, resulting in a total of 5 rounds. MEPS is a nationally representative sample of the U.S. civilian noninstitutionalized population, sponsored by the Agency for Health Care Research and Quality and the Centers for Disease Control and Prevention. In the present study, the analytic sample, based on the baseline (round 1) interview, consisted of 7404 (61%) of the 12,170 adults aged 65–85 years who self-reported that a physician or other health professional told them they had "hypertension, also called high blood pressure." Of the group diagnosed with hypertension, we took the subset of 536 persons who reported COPD at the baseline interview and had two years of complete follow-up data. COPD was identified as self-reporting that a physician or other health professional told them they had chronic bronchitis (present in the 12 months before baseline) or emphysema (ever diagnosed). These two conditions (hypertension and COPD) were chosen because persons with MCCs are more likely to concomitantly use five or more medications. As the study used existing deidentified data that were publicly available, it was granted exemption from participant consent as documented in Human Investigation Committee Protocol Number 1510016585 at the Yale School of Medicine.

Concurrent outcomes: limitations in social activity and mobility within a one-year period

The social activity outcome ($SocLim_{ij}$), where subscripts i and j, respectively, signify the person and year, indicated whether the person had reported, because of an impairment or a physical or mental health problem, limitations in their social activity at each one-year follow-up interview. The second outcome ($MobLim_{ij}$) was an indicator of whether the person had difficulty in walking, climbing stairs, grasping objects, reaching overhead, lifting, bending, or stooping or standing for long periods of time in the same two single-year periods in which they were concurrently at risk for the first outcome.

Exposure (polypharmacy) and covariates (age, gender, and arthritis)

To simplify the illustration of PCR and TCR in a relevant subset of the study population, the outcome model terms were restricted to the exposure, that is, an indicator of polypharmacy (T_{ij}) and the covariates of age in years, arthritis, and sex, each of which is associated with at least one of the outcomes.

Joint modeling of the concurrent binary outcomes

We used a shared random intercept joint model of the pair of longitudinal, binary outcomes to examine how strongly their PCRs and TCRs were affected by polypharmacy after adjustment for age, arthritis, and sex [19]. The model is defined as follows:

$$\begin{aligned}\text{Prob}\left(SocLim_{ij}=\ 1|P_i,\mu_i,age_{ij},arthritis_{ij},female_i\right)&=\varphi\left(\beta_{01}+\beta_{T_1}T_{ij}+\beta_{1age}age_{ij}\ +\beta_{1arth}arthritis_{ij}\ +\beta_{1fem}female_i+\ \mu_i\right),\\ \text{Prob}\left(MobLim_{ij}=\ 1|P_i,\mu_i,age_{ij},arthritis_{ij},female_i\right)&=\varphi\left(\beta_{02}+\beta_{T_2}T_{ij}+\beta_{2age}age_{ij}\ +\beta_{2arth}arthritis_{ij}\ +\beta_{2fem}female_i+\ \mu_i\right)\end{aligned}\tag{1}$$

where P_i is each person's IPTW at the baseline interview. The P_i was used to balance the confounders in the two levels of exposure (those with and without polypharmacy) and were estimated from a logistic regression model, in which polypharmacy was regressed on demographic and clinical measures, using backward selection with a p-value of 0.20 for retention. The final variables retained included longest duration of any hypertension medication in years, age, presence of angina, presence of arthritis, presence of asthma, presence of diabetes, sex, and any need for an assistive device. The $\mu_i \sim N(0,\sigma_u^2)$ in Model (1) represents each person's random intercept that, by capturing unobserved patient characteristics, discerns that individual's likelihood for the pair of outcomes from those of the typical values of the entire study population; T_{ij} indicates polypharmacy for individual i at year j; ϕ is the inverse logit link function; β_{01} *and* β_{02} are the intercepts, β_{T_1} and β_{T_2} quantify the outcome-specific associations of polypharmacy, and the other model terms represent the outcome-specific associations of the covariates. The probabilities defined in Model (1) are the

PCRs of each outcome over the one-year period that starts at the time that the explanatory variables are updated. The corresponding TCRs are the corresponding probabilities derived by setting the person-specific intercept (μ_i) to zero.

Descriptive statistics of the concurrent risk for each outcome

We define PCR as the subject-specific probability of an index outcome within a defined interval of time, while currently at risk for a separate outcome, where the outcomes are not mutually exclusive and can be jointly modeled with a shared random intercept. We further define TCR as the risk obtained by setting the random intercept to null. We used Model (1) to calculate the PCRs and TCRs for the concurrent outcomes of limitations in social activity and mobility for all persons in the study. We subsequently calculated descriptive statistics of the PCRs and TCRs of persons with and without polypharmacy in the overall sample.

Contrasting PCR and TCR among an illustrative subgroup of women aged 85 years with arthritis and polypharmacy

As participants in this MEPS sample have MCCs, there will be a spectrum of PCRs for participants and TCRs for each of the concurrent outcomes, reflecting the wide-ranging variability of polypharmacy's influence. To illustrate the variability of the PCRs relative to the TCR, we have chosen an illustrative subset consisting of women aged 85 years with arthritis and polypharmacy, which comprises 12 persons. For these persons, we display their person-specific random intercepts, as well as their outcome-specific PCRs in relation to their corresponding TCRs.

Table 1
Baseline characteristics of participants from the Medical Expenditure Panel Survey 2008 to 2013 panels of adults with hypertension and chronic obstructive pulmonary disease by polypharmacy ($n = 536$)

Participant characteristics	Polypharmacy	
	<5 classes of medications ($n = 159$) $n = 158$ (29.6%)	≥5 classes of medications ($n = 377$) (70.4%)
	n (%)	*n* (%)
Sociodemographic		
Age*: ≥75 versus 65–74	75 (47.2)	161 (42.7)
Female*	88 (55.4)	232 (61.5)
African-American	35 (22.0)	78 (20.7)
Hispanic ethnicity	15 (9.4)	52 (13.8)
Education (≥ 12 y)	111 (69.8)	249 (66.2)
Medical conditions		
Angina*	16 (10.1)	67 (17.8)
Arthritis*	102 (64.2)	284 (75.3)
Asthma*	19 (12.0)	99 (26.3)
Cancer	27 (17.0)	60 (15.9)
Coronary heart disease	37 (23.3)	135 (35.8)
Cognitive impairment	21 (13.2)	60 (16.0)
Diabetes*	30 (18.9)	149 (39.5)
Myocardial infarction	24 (15.1)	80 (21.2)
Stroke	22 (13.8)	73 (19.4)
Use of assistive device*	41 (25.8)	138 (36.6)
Duration of antihypertensive use*		
No treatment	78 (49.1)	37 (9.8)
Do not know	10 (6.3)	53 (14.1)
≤ 1 y	14 (8.8)	37 (9.8)
2–5 y	21 (13.2)	86 (22.8)
6–10 y	18 (11.3)	65 (17.2)
>10 y	18 (11.3)	99 (26.3)

* Included in propensity model of baseline polypharmacy.

Results

Characteristics of participants with and without polypharmacy

Table 1 provides descriptive statistics of the study sample by polypharmacy status. In the study sample, 70% had polypharmacy, the mean age was 73.7 years (95% confidence interval [CI]: 73.4, 74.1), 60% were female, and 72% had arthritis.

There are some notable differences that are reasonable, given that persons with MCCs are likely to have polypharmacy. The prevalence of both diabetes and asthma is greater among those with polypharmacy (39.5% and 26.3%, respectively) than among those without (18.9% and 12.0%, respectively). There is also a higher prevalence of four vascular conditions among those with polypharmacy. Regarding use of antihypertensive medication, just over half (50.9) of those without polypharmacy were taking an antihypertensive compared with 90.2% of those with polypharmacy, whereas the proportion of persons taking an antihypertensive for two years or longer was nearly double among those with polypharmacy. The imbalance in chronic conditions documented in Table 1 justifies the use of the IPTWs in the joint model to provide a more rigorous evaluation of the outcomes' associations with polypharmacy. Figure 1 shows that across the quartiles of the propensity scores in the pseudopopulation analytic sample in the weighted model, those with and without polypharmacy are well balanced regarding the confounders.

At year one, 123 (23.0%) participants reported a social limitation, whereas 289 (53.9%) participants reported mobility difficulties. The usefulness of a joint model for the social and mobility limitation outcomes is reflected in the 0.42 correlation between the two outcomes at year one, with 114 (21.3%) of the 536 participants reporting both outcomes. In year two, the outcomes exhibited comparable correlation of 0.45.

Jointly modeled parameters

Table 2 presents the separately and jointly modeled parameter estimates for the concurrent outcomes. For all significant associations, the jointly modeled coefficients are attenuated with respect to their separately modeled counterparts, justifying the added complexity of the joint model pursuant to calculating accurate estimates of the PCR and TCR. Because of this, we restrict our comments to the coefficients estimated from the joint model. For limitation in social activity, polypharmacy and arthritis were, respectively, associated with odds ratios of 2.0 (95% CI: 1.2, 3.5) and 3.9 (95% CI: 2.0, 7.9). For limitation in mobility, age in years, arthritis, and female gender were, respectively, associated with odd ratios of 1.1 (95% CI: 1.0, 1.1), 3.7 (95% CI: 2.0–6.6), and 4.3 (95% CI: 2.1, 8.8).

Ranges of TCRs and PCRs of the study sample ($N = 536$)

The jointly estimated parameters in the bottom half of Table 2 were used to calculate the PCRs and TCRs for the two outcomes for all persons. We summarize their respective ranges in strata defined by polypharmacy. For limitation in social activity among those without polypharmacy, the TCRs range from 1.0% to 5.4%. These values indicate that the typical probability of this outcome is low, in stark contrast with the PCRs that range from 0.0% to 96.3%, reflecting great individual heterogeneity. For limitation in social activity among those with polypharmacy, the TCRs range from 2.0% to 10.4%, suggesting that the typical probability of this outcome is nearly double relative to those without polypharmacy, whereas the range of the PCRs, from 0.1% to 96.1%, was nearly identical to that for persons without polypharmacy.

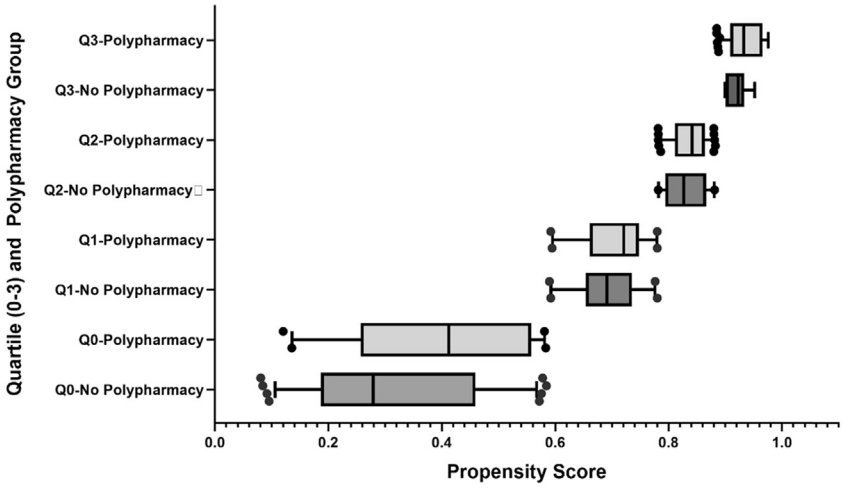

Fig. 1. Distribution of propensity by quartile and polypharmacy group.

For limitation in mobility among those without polypharmacy, the TCRs range from 8.2% to 82.2% and the corresponding PCRs range from 1.2% to 99.9%. For limitation in mobility among those with polypharmacy, the TCRs range from 10.3% to 85.5%, suggesting that the typical probability of this outcome also varies greatly among persons with polypharmacy. The corresponding PCRs, ranging from 2.0% to 99.8%, reflect even greater heterogeneity.

PCRs and TCRs among women aged 85 years with arthritis and polypharmacy

Table 3 presents the person-specific intercepts, the individual PCRs, and the TCR for the concurrent outcomes of limitations in social activity and mobility, for 12 women aged 85 years with arthritis and polypharmacy. For limitations in social activity, the PCRs range from 0.2% to 83.6%, with eight PCRs exhibiting values greater than the common TCR of 7.3%. In contrast, the TCR indicates that very few of these women typically experience a limitation in their social activity.

For limitations in mobility, the PCRs range from 13.9% to 99.7%, again with the same eight women exhibiting PCRs greater than the common TCR of 85.5%. The TCR indicates that nearly all these women can be expected to have some limitation of mobility based on their covariates, whereas the PCR shows the great heterogeneity within this group. Because the person-specific intercepts of these 12 women are shared in the joint model of the concurrent outcomes, these women, when ranked in increasing magnitude of PCRs, exhibit identical ordering for both outcomes. This illustrates the overriding strength of the individual-specific differences (i.e. person-specific intercept) in determining the magnitude of the PCRs.

Figure 2 depicts the PCRs and TCRs of all 12 women in the subset of interest. The top panel presents the one-year probabilities of limitations in social activity, whereas those corresponding to limitations in mobility are in the bottom panel. The center panel presents an idealized normal distribution of all the person-specific random intercepts where the vertical dash-dotted line in the middle indicates the mean and where each number centered on a vertically dotted line gives the rank of that person's random intercept within the study sample ($n = 536$). The filled-in dots are the PCRs of the individuals where the dashed horizontal lines represent the TCR of each outcome. Starting from the top, the TCR of limitation in social activity is only 7.3%, meaning this outcome is relatively rare in our subgroup. Nonetheless, the PCRs span from near zero to greater than 80%, demonstrating wide-ranging heterogeneity within this small subgroup. The ranks of the person-specific random intercepts range from 15 through 498 (out of 536 persons), thereby spanning the great majority of the study sample distribution. Regarding limitations in mobility, the TCR is 85.5%, meaning that most of the subgroup experience this outcome. Accordingly, only one woman has a PCR <50% and eight have PCRs higher than the TCR, with the five highest values approximating 100%. The PCRs for each pair of outcomes uniformly ascend with the corresponding rank of the person-specific random intercepts.

Table 2
Odds ratios for separately and jointly modeled limitations in social activity and mobility over two single-year follow-up periods

Characteristic	Social activity limitation			Mobility limitation		
	Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value
Separate outcome models with person-specific random intercept and inverse probability of treatment weighting						
Polypharmacy: (≥ 5 classes of medications)	2.38	1.09–5.18	.029	1.27	0.74–2.19	.384
Age in years	1.04	0.95–1.13	.420	1.18	1.09–1.28	<.001
Arthritis	7.49	2.50–22.38	<.001	5.52	2.56–11.89	<.001
Female	0.77	0.26–2.28	.632	7.83	2.60–23.59	<.001
Joint outcome models with shared person-specific random intercept and inverse probability of treatment weighting						
Polypharmacy: (≥ 5 classes of medications)	2.02	1.18–3.46	.011	1.27	0.82–1.98	.280
Age in years	0.99	0.94–1.05	.801	1.06	1.00–1.12	.035
Arthritis	3.93	1.97–7.87	<.001	3.69	2.05–6.63	<.001
Female	0.78	0.37–1.63	.508	4.30	2.09–8.85	<.001

Based on data from the Medical Expenditure Panel Survey 2008 to 2013 panels of adults with hypertension and chronic obstructive pulmonary disease.

Table 3
Personalized concurrent risk and typical concurrent risk of 85-year-old females in the Medical Expenditure Panel Survey (2008–2013) with arthritis, chronic obstructive pulmonary disease, hypertension, and polypharmacy

Study ID	Random intercept	PCRs of concurrent outcomes	
		Limitation in social activity (TCR = 7.3%)	Limitation in mobility (TCR = 85.5%)
1	−3.60	0.2	13.9
2	−1.61	1.6	54.2
3	−1.58	1.6	54.7
4	−1.57	1.6	55.2
5	0.31	9.7	89.0
6	0.32	9.7	89.0
7	0.32	9.8	89.1
8	2.24	42.6	98.2
9	2.27	43.2	98.3
10	2.30	44.0	98.3
11	4.17	83.6	99.7
12	4.17	83.6	99.7

ID = identification number.

Discussion

Epidemiological studies have historically presented findings on multiple outcomes without considering how the outcomes may co-inform each other. Although the associations of explanatory variables with these multiple outcomes may be adjusted for multiple comparisons, such adjustment does not share information across outcomes at the participant level. Furthermore, as we move to the era of personalized medicine, it is helpful to model the person-specific effects, in part to address the HTE among individuals. It is helpful to understand the role of HTE within the broader context of MCCs, which increases health care utilization and compromise adherence to medication and other therapeutic regimens [16,20–24]. For these reasons, the identification of treatments that

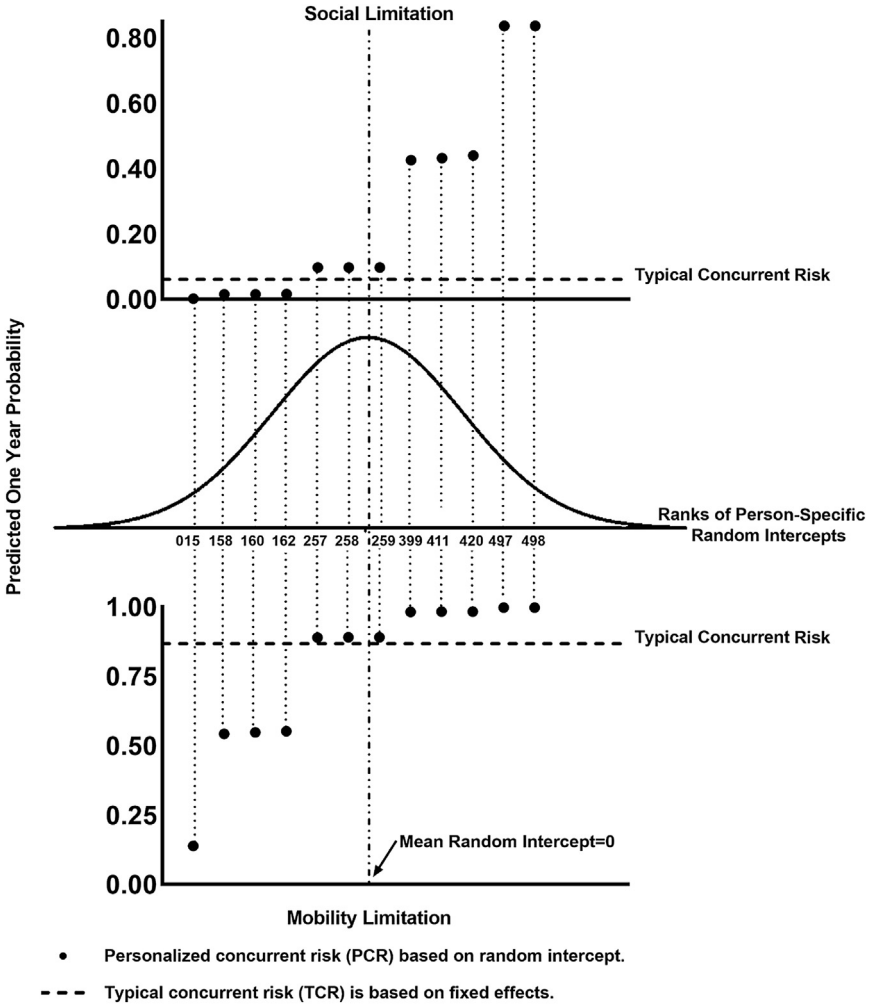

Fig. 2. Personalized concurrent risk (PCR) and typical concurrent risk (TCR) among 85-year-old women with arthritis and polypharmacy ($n = 12$).

improve outcomes of persons with multiple diseases is a vital area of medical research [25–28]. Further attesting to MCC's relation to HTE, it has been reported that MCCs affect the prognoses of heart disease, diabetes, and cancer [28, 29]. Compelling research also documents the adverse effect of MCCs on three of the most important patient-centered outcomes, namely, survival, functional ability, and quality of life [30–36].

We demonstrated that joint modeling of concurrent limitations in social activity and mobility over two consecutive calendar years has allowed the calculation of the PCRs and TCRs for these outcomes, which clearly displays the HTE at the individual level. Although the first outcome is relatively rare, the PCRs of the 12 individual women of age 85 years with arthritis and polypharmacy in our illustration exhibited a wide range of heterogeneity. The second outcome of limitation in mobility was common but also exhibited considerable heterogeneity. The calculation of PCRs is conditional on having longitudinal data for the individual characteristics, whereas the TCR represents the typical probability of those individuals over the same period. The magnitude of the person-specific intercept, which is shared by the outcomes, drives the relative magnitude of the PCRs, whereas the TCR can be obtained by setting the person-specific intercept to zero. Estimates of PCR and TCR can be calculated from national or institutional data sets and may facilitate the practice of personalized care.

A primary limitation of modeling concurrent binary outcomes is that the marginal correlation between the outcomes is bounded [37]. There are two related limitations that help explain the wide-ranging personalized effect sizes in our example. First, binary outcomes are notoriously inefficient in terms of providing information with which to calculate associations. Second, our data constraint of having only two repeated measures with which to estimate person-specific random intercepts produced limited granularity in their magnitudes. However, given the paucity of published examples of joint modeling of concurrent binary outcomes, and the demonstrated attenuation of the jointly estimated coefficients (relative to separate outcome models) for important covariates, this application is novel and informative. Because there were 47 participants (8%) who did not have the year two interview, we restricted our illustrative example to fixed covariates, complete case data, and correlated outcomes important to persons with MCCs. However, this method can accommodate time-varying covariates and missing data methods. Although this example is not intended to imply causation or an exhaustive treatment of covariates, our use of IPTWs in the context of a joint model is likely to have reduced bias in the estimates.

Two recent publications provide potential applications of the technique. Fernando et al [38] examined and compared the Charlson Comorbidity Index and the Elixhauser Comorbidity Measure and their associations with mortality, development of complications, and daily use of additional services in the intensive care unit. The modeling approach described here would allow the joint modeling of daily development of complications and daily use of additional intensive care unit services and could help evaluate whether the Charlson Comorbidity Index and the Elixhauser Comorbidity Measure have distinct or complementary associations with this pair of concurrent outcomes. Glymour et al [39] examine use of antidepressant medication and risk of incident stroke. Joint longitudinal modeling of the occurrence of stroke and of major depressive disorder could help evaluate the potential trade-offs between treatment of depression and potential elevation of risk for stroke.

Future research to extend this joint modeling approach should include combinations of outcomes of other distributional forms, such as counts or ordinal categories, use of more than two outcomes, and the incorporation of methods for missing data.

Acknowledgment

This work was supported by grants from the U.S. National Institute on Aging, United States at the National Institutes of Health, United States (grants R01 AG047891, P30AG021342-16S1).

References

[1] Anderson G. Making the Case for Ongoing Care. Princeton, NJ: Robert Wood Johnson Foundation; 2010. http://www.rwjf.org/en/research-publications/find-rwjf-research/2010/02/chronic-care.html. [Accessed 23 August 2019].
[2] Multiple Chronic Conditions-A Strategic Framework. Washington DC: U.S. Department of Health and Human Services; 2010. https://www.hhs.gov/sites/default/files/ash/initiatives/mcc/mcc_framework.pdf. [Accessed 23 August 2019].
[3] Fried TR, Bradley EH, Towle VR, Allore H. Understanding the treatment preferences of seriously ill patients. N Engl J Med 2002;346(14):1061–6.
[4] McNeil BJ, Pauker SG, Sox Jr HC, Tversky A. On the elicitation of preferences for alternative therapies. N Engl J Med 1982;306(21):1259–62.
[5] Cauley JA, Ensrud KE. Considering competing risks . . . Not all black and white. Arch Intern Med 2008;168(8):793–5.
[6] Crossing the quality chasm: A new health system for the 21st century. Washington, D.C.: National Academies Press; 2001.
[7] Akishita M, Ishii S, Kojima T, Kozaki K, Kuzuya M, Arai H, et al. Priorities of health care outcomes for the elderly. J Am Med Dir Assoc 2013;14(7):479–84.
[8] Tinetti ME, Naik AD, Dodson JA. Moving from disease-centered to patient goals-directed care for patients with multiple chronic conditions: patient value-based care. JAMA Cardiol 2016;1(1):9–10.
[9] Agogo GO, Murphy TE, McAvay GJ, Allore HG. Joint modeling of concurrent binary outcomes in a longitudinal observational study using inverse probability of treatment weighting for treatment effect estimation. Ann Epidemiol 2019;35:53–8.
[10] Thomas M, Halpin DM, Miravitlles M. When is dual bronchodilation indicated in COPD? Int J Chron Obstruct Pulmon Dis 2017;12:2291–305.
[11] Gnjidic D, Hilmer SN, Blyth FM, Naganathan V, Waite L, Seibel MJ, et al. Polypharmacy cutoff and outcomes: five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. J Clin Epidemiol 2012;65(9):989–95.
[12] Langeard A, Pothier K, Morello R, Lelong-Boulouard V, Lescure P, Bocca ML, et al. Polypharmacy Cut-Off for Gait and Cognitive Impairments. Front Pharmacol 2016;7:296.
[13] Hilmer SN, Gnjidic D. The effects of polypharmacy in older adults. Clin Pharmacol Ther 2009;85(1):86–8.
[14] Jyrkka J, Enlund H, Korhonen MJ, Sulkava R, Hartikainen S. Polypharmacy status as an indicator of mortality in an elderly population. Drugs Aging 2009;26(12):1039–48.
[15] Olsson IN, Runnamo R, Engfeldt P. Medication quality and quality of life in the elderly, a cohort study. Health Qual Life Outcomes 2011;9:95.
[16] Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. JAMA 2005;294(6):716–24.
[17] Benichou J, Gail MH. Estimates of absolute cause-specific risk in cohort studies. Biometrics 1990;46(3):813–26.
[18] Gail MH, Costantino JP, Bryant J, Croyle R, Freedman L, Helzlsouer K, et al. Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer. J Natl Cancer Inst 1999;91(21):1829–46.
[19] Murphy TE, McAvay GJ, Allore HG, Stamm JA, Simonelli PF. Contributions of COPD, asthma, and ten comorbid conditions to health care utilization and patient-centered outcomes among US adults with obstructive airway disease. Int J Chron Obstruct Pulmon Dis 2017;12:2515–22.
[20] Tooth L, Hockey R, Byles J, Dobson A. Weighted multimorbidity indexes predicted mortality, health service use, and health-related quality of life in older women. J Clin Epidemiol 2008;61(2):151–9.
[21] Condelius A, Edberg AK, Jakobsson U, Hallberg IR. Hospital admissions among people 65+ related to multimorbidity, municipal and outpatient care. Arch Gerontol Geriatr 2008;46(1):41–55.
[22] Laux G, Kuehlein T, Rosemann T, Szecsenyi J. Co- and multimorbidity patterns in primary care based on episodes of care: results from the German CONTENT project. BMC Health Serv Res 2008;8:14.
[23] Tinetti ME, Fried T. The end of the disease era. Am J Med 2004;116(3):179–85.
[24] Tinetti ME, Bogardus Jr ST, Agostini JV. Potential pitfalls of disease-specific guidelines for patients with multiple conditions. N Engl J Med 2004;351(27):2870–4.
[25] Boyd CM, Boult C, Shadmi E, Leff B, Brager R, Dunbar L, et al. Guided care for multimorbid older adults. Gerontologist 2007;47(5):697–704.
[26] McCormick WC, Boling PA. Multimorbidity and a comprehensive Medicare care-coordination benefit. J Am Geriatr Soc 2005;53(12):2227–8.
[27] Noel PH, Frueh BC, Larme AC, Pugh JA. Collaborative care needs and preferences of primary care patients with multimorbidity. Health Expect 2005;8(1):54–63.
[28] Muller-Tasch T, Peters-Klimm F, Schellberg D, Holzapfel N, Barth A, Junger J, et al. Depression is a major determinant of quality of life in patients with

chronic systolic heart failure in general practice. J Card Fail 2007;13(10):818–24.
[29] Gross CP, Guo Z, McAvay GJ, Allore HG, Young M, Tinetti ME. Multimorbidity and survival in older persons with colorectal cancer. J Am Geriatr Soc 2006;54(12):1898–904.
[30] Lee SJ, Lindquist K, Segal MR, Covinsky KE. Development and validation of a prognostic index for 4-year mortality in older adults. JAMA 2006;295(7):801–8.
[31] Fried LP, Kronmal RA, Newman AB, Bild DE, Mittelmark MB, Polak JF, et al. Risk factors for 5-year mortality in older adults: the Cardiovascular Health Study. JAMA 1998;279(8):585–92.
[32] 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). J Clin Epidemiol 2001;54(7):680–6.
[33] Kadam UT, Croft PR. Clinical multimorbidity and physical function in older adults: a record and health status linkage study in general practice. Fam Pract 2007;24(5):412–9.
[34] Fortin M, Lapointe L, Hudon C, Vanasse A, Ntetu AL, Maltais D. Multimorbidity and quality of life in primary care: a systematic review. Health Qual Life Outcomes 2004;2:51.
[35] Fortin M, Bravo G, Hudon C, Lapointe L, Dubois MF, Almirall J. Psychological distress and multimorbidity in primary care. Ann Fam Med 2006;4(5):417–22.
[36] John R, Kerby DS, Hennessy CH. Patterns and impact of comorbidity and multimorbidity among community-resident American Indian elders. Gerontologist 2003;43(5):649–60.
[37] Frechet M. Sur les tableaux de correlation dont les marges sont donnees. Ann de l'Universite de Lyon Section A 1951;14:53–77.
[38] Fernando DT, Berecki-Gisolf J, Newstead S, Ansari Z. Effect of comorbidity on injury outcomes: a review of existing indices. Ann Epidemiol 2019.
[39] Glymour MM, Gibbons LE, Gilsanz P, Gross AL, Mez J, Brewster PW, et al. Initiation of antidepressant medication and risk of incident stroke: using the Adult Changes in Thought cohort to address time-varying confounding. Ann Epidemiol 2019;35:42–47.e1.