Polypharmacy and its association with dementia, Parkinson's Disease and mortality risk in UK adults: a multistate modeling approach

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ONLINE SUPPLEMENTARY METHODS 1

Detailed steps of the multistate modeling process are provided below along with description of sensitivity analyses: (i) We utilized Stata's *msset* command to arrange our dataset, incorporating 3 events of interest along with their corresponding age at occurrence. Additionally, we specified the age at baseline assessment, which corresponds to the initial instance of the UKB dataset. Events included incidence of PD or dementia, and death from any cause (considered as the last event). Individuals who did not experience any events were classified as "healthy." A transition transformation matrix was produced using the *msboxes* command, which included a multistate set of boxes with four states: "Healthy", "PD", "Dementia", and "Deaths." (ii) The data was subsequently organized in long format for all 3 events combined, using _trans1 through $\_trans_k$ to isolate each transition from the identified group of k transitions. (iii) The Aalen-Johansen estimates of transition probabilities were calculated, together with their 95% confidence intervals. These estimates represent the likelihood of being in each of the four states as age progresses, as well as the likelihood of transitioning from PD and Dementia to other states. The *msaj* command was employed for this purpose. The data points were graphically represented using line plots with step functions (1).

(iv) Parametric survival models were estimated using POLYPH as the primary variable of interest. The potentially confounding factors included age at baseline, sex, race (Non-White vs. White), household size, TDI z-score, SES_{res}, LE8zrev, the co-morbidity index and self-rated health. The models were primarily based on the Weibull distribution and were constructed using the *stmerlin* command (2). The efficacy of this parametric model was subsequently assessed by comparing it to alternative models employing different distributions (see to **supplemental Table 1** for further information). The model with the lowest AIC and/or BIC was compared to the Weibull model in order to assess the relationship between the TDI z-score and the outcome of interest. The models are constructed for every identified *k* transition. Among other alternatives, the Royston-Parmar flexible parametric model was also taken into consideration (3). (v) Survival probabilities were estimated for each transition and associated model. The estimation was done

twice: first without considering covariates, and second by assigning values of POLYPH as either 0 (indicating 0-1 medications used) or 1 (indicating 2+ medications used). The estimation was performed using the *stmerlin* postestimation predict command and options, with a Weibull distribution (2). The model-based estimated survival probabilities for each transition were shown, together with their 95% confidence intervals, using Kernel-weighted local polynomial smoothing throughout the age of follow-up (4). By extending the age at follow-up to 80 years, we were able to estimate the difference in survival probability between individuals who screen negative vs. positive for POLYPH for each transition. The prediction was accompanied by a 95% confidence interval (2). We applied a comparable smoothing technique using local polynomials on baseline age values that were limited to a range of 50 years to 79 years (4). Greenwood pointwise standard errors were computed to determine the predicted survival probabilities and differences in survival probability (2). The study provides descriptive statistics, including the median and interquartile range (IQR), for point estimates. These statistics are reported mainly for the predicted differences at age 80y for each transition.

(vi) Furthermore, a sensitivity analysis was performed to compare the fully adjusted parametric model with different distributional specifications.

(vii) In order to examine further which groups of medications were explaining any association between exposure and outcome, UKB field 20003 was used for instance 0 (or baseline assessment) covering an array of 48 possible specific medications. The most commonly used medications were defined by an overall frequency of 5000 or more in the entire UK Biobank study (i.e. out of the 500K participants). These data were used to conduct a latent class analysis (LCA) and generate probabilities of membership in each of these latent classes. These probabilities of group membership were then labelled based on their relationship to the selected medications used and heatmaps were used for visualization. Importantly, they were entered into a mediation analysis whereby POLYPH was the main exposure, each latent class group membership probability (converted to Ln(odds)) was one of several mediators, and the outcome was the time-to-event to each of uncovered health state transitions. This analysis was conducted using generalized structural

equations (GSEM) models, in an attempt to explain detected associations between POLYPH^{+} and any of the outcomes of interest at a type I error of 0.05. Exogenous variables in the GSEM model included all potentially confounding covariates listed below in the "Covariates" section. More details regarding both the LCA and GSEM are provided in **supplementary Method 2**.

(viii) A secondary definition for POLYPH with a threshold of 5^{+} medications instead of 2^{+}, was used in part of the analysis, namely for part iv and vii.

Supplementary Table 1.

Model	Description
Weibull Distribution	Models failure times characterized by a monotonic hazard function. The shape parameter (β) allows flexibility.
Exponential Distribution	Models constant hazard over time, with a memoryless property such that future survival depends only on the current time.
Gompertz Distribution	Models a hazard that increases exponentially over time. Useful for biological processes with aging effects.
Piecewise Exponential with 3 Knots	Models the hazard rate as constant within predefined intervals (knots), allowing for different hazard rates in each interval.
Restricted Piecewise	Similar to the piecewise exponential model but with the constraint that hazard rates do not increase across intervals.
Restricted Cubic Spline	Models complex hazard functions with smooth transitions between segments defined by knots, offering greater flexibility.

Supplementary Table 2. Parametric survival models for the association between POLYPH^{2+} and six transitions between four states (healthy, PD, dementia, and death): UK Biobank 2006-2021[a]

	Transition 1 Healthy→PD	Transition 2 Healthy→Dementia	Transition 3 Healthy→Mortality	Transition 4 PD→Dementia	Transition 5 PD→Mortality	Transition 6 Dementia→Mortality
Model	Coef (SE) [P]	Coef (SE) [P]	Coef (SE) [P]	Coef (SE) [P]	Coef (SE) [P]	Coef (SE) [P]
Weibull Distribution	0.075 (0.049) [0.13] BIC=39206	0.138 (0.034) [**<0.001**] BIC=77892	0.105 (0.015) [**<0.001**] BIC= 325286	0.032(0.143) [0.82] BIC=2615	-0.013 (0.105) [0.91] BIC=3971	0.083(0.053) [0.11] BIC= 13309
Exponential Distribution	0.108 (0.05) **[0.028]** BIC=48853	0.179 (0.034) [**<0.001**] BIC=102895	0.132 (0.015) [**<0.001**] BIC= 426575	0.047(0.143) [0.75] BIC= 2621	0.005 (0.105) [0.96] BIC=3987	0.094 (0.053) [0.075] BIC=13329
Gompertz Distribution	0.073 (0.049) [0.14] BIC=39274	0.136 (0.034) [**<0.001**] BIC=77931	0.103 (0.015) [<0.001] BIC= 32581	0.032(0.143) [0.83] BIC=2616	-0.014(0.105) [0.89] BIC= 3969	0.083 (0.053) [0.12] BIC=13308
Piecewise Exponential with 3 Knots	0.108 (0.049) **[0.028]** BIC=49670	0.179 (0.034) [**<0.001**] BIC=102452	0.132 (0.015) [**<0.001**] BIC= 424280	0.047(0.144) [0.75] BIC= 2621	0.005 (0.105) [0.96] BIC=3987	0.094 (0.053) [0.075] BIC=13329
Restricted Piecewise	0.083 (0.049) [0.093] BIC=39052	0.144 (0.033) [**<0.001**] BIC=77636	0.111 (0.015) [**<0.001**] BIC= 322563	0.036(0.143) [0.80] BIC= 2637	-0.019 (0.106) [0.86] BIC= 3987	0.082 (0.053) [0.12] BIC=13333
Restricted Cubic Spline	0.082 (0.049) [0.096] BIC=39057	0.144 (0.034) [**<0.001**] BIC=77648	0.110 (0.015) [**<0.001**] BIC=322741	0.034(0.143) [0.81] BIC= 2637	-0.017 (0.105) [0.87] BIC=3988	0.083 (0.052) [0.12] BIC= 13334

Abbreviations: BIC=Bayesian Information Criterion; Coef = Coefficient; $LE8_{zrev}$=z-scored Life's Essential 8 total score, multiplied by -1; P = p-value; PD = Parkinson's Disease; POLYPH=Polypharmacy; SE = standard error; SESres=residual from linear regression of SES z-score on TDI z-score; TDI=Townsend Deprivation Index; UK=United Kingdom.

[a] All parametric survival models adjusted for age, sex, race, SES_{res} , TDI, household size, and $LE8_{zrev}$. Values are estimated Log_e(HR) with SE and associated p-value for null hypothesis that Log_e(HR)=0. Alternative distributions were tested and compared using BIC.

Supplementary Table 3. Descriptives of predicted differences (medians of prediction, lower 95% CI limit and upper 95% CI limit) in survival probability for each of 6 transitions, comparing $POLYPH^{-}$ vs. $POLYPH^{+}$ with age at event set at 80y[a]

	Transition 1	Transition 2	Transition 3	Transition 4	Transition 5	Transition 6
	"Healthy"→ PD	"Healthy" → Dementia	"Healthy"→ Death	PD→Dementia	PD→Death	Dementia→Death
Prediction	+0.0019	0.0080	0.019	+0.011	-0.004	+0.005
LCL	-0.0005	0.0041	0.014	-0.088	-0.075	-0.003
UCL	+0.0043	0.012	0.024	+0.111	+0.066	+0.014

[a] *Based on fully adjusted Weibull model with POLYPH as main exposure, and adjusted for age, sex, race, household size, TDI z-score, SESres, and LE8zrev.*

Abbreviations: PD = Parkinson's Disease; POLYPH=Polypharmacy; SD=Standard Deviation; SE = standard error; TDI=Townsend Deprivation Index; UK=United Kingdom.

ONLINE SUPPLEMENTARY METHODS 2. Latent class analysis and generalized SEM

Latent class analysis in R

Latent Class Analysis (LCA) is a statistical method employed to discern concealed classes within a population through observed categorical data(5, 6, 7). The *poLCA* package in R offers an extensive array of tools for estimating latent class models, enabling users to specify the required number of classes, apply the model to the dataset, and evaluate its fit using metrics such as the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC)(5, 6, 7). The *poLCA* function streamlines model specification by enabling users to delineate the formula for observable variables and the quantity of classes(5, 6, 7). The system employs Expectation-Maximization (EM) techniques to determine the probability of class membership and item answers(5, 6, 7). The application additionally incorporates visualization tools for analysis(5, 6, 7). Below are the key equations on the basis of which latent class analysis for medication use class membership is determined, assuming a total of *J* medications that were considered commonly used based on a cutoff for frequency of 5,000 in the largest possible UKB sample.

(Eq. 1.1) *Latent class probabilities*:

$$\boldsymbol{P(Z_i = k) = \pi_k}$$

(Eq. 1.2) *Conditional probabilities*:

$$P(X_{ij=x} |\, Z_i = k) = \theta_{jk}(x)$$

(Eq. 1.3) *Joint probability*:

$$\boldsymbol{P(X_i | Z_i = k\,) = \prod_{j=1}^{J} P(X_{ij}\,| Z_i = k)}$$

(Eq. 1.4) *Marginal likelihood*:

$$\boldsymbol{P(X_i) = \sum_{k-1}^{K} \pi_K \prod_{j=1}^{J} P(X_{ij} \mid Z_I = k \ )}$$

(Eq. 1.5) *Log-likelihood*:

$$\boldsymbol{L(\theta) = \sum_{i-1}^{N} log(\sum_{k-1}^{K} \pi_k \prod_{j=1}^{J} P(X_{ij} \mid Z_i \ = \ k)}$$

(Eq. 1.6) *Posterior probability of class membership*:

$$P(Z_i \ = k \mid X_i) = \frac{\pi_k \prod_{j=1}^{J} P(X_{ij} \mid Z_i = k)}{\sum_{k=1}^{K} \pi_k \prod_{j=1}^{J} P(X_{ij} \mid Z_i = k)}$$

Generalized SEM in Stata

This appendix offers an elaborate manual on performing Generalized Structural Equation Modeling (SEM) in Stata, with the condition that the ultimate outcome Y adheres to a Weibull distribution. The model comprises a primary binary exposure variable X, a continuous mediator M, and many exogenous variables Zi, which are permitted to predict the ultimate outcome, the mediator, and the primary exposure variable.

1. Model Specification

The generalized SEM can be conceptualized with the following structure:

1. **Final Outcome Model:**

$$Y \sim \text{Weibull}(\lambda, k)$$

$$\log(\lambda) = \beta_0 + \beta_1 X + \beta_2 M + \sum_{i=1}^{p} \beta_{2+i} Z_i$$

2. **Mediator Model:**

$$\Pr(M = 1) = \frac{\exp(\gamma_0 + \gamma_1 X + \sum_{i=1}^{p} \gamma_{1+i} Z_i)}{1 + \exp(\gamma_0 + \gamma_1 X + \sum_{i=1}^{p} \gamma_{1+i} Z_i)}$$

3. **Exposure Model:**

$$\Pr(X = 1) = \frac{\exp(\delta_0 + \sum_{i=1}^{p} \delta_i Z_i)}{1 + \exp(\delta_0 + \sum_{i=1}^{p} \delta_i Z_i)}$$

Here, λ is the scale parameter controls the expected survival time, and log(λ) is the log of time to event, k is the shape parameter of the Weibull distribution, β, γ, and δ are the coefficients, and ϵ_M is the error term for the mediator.

In hazard function formulation, the Weibull model is as follows:

$$h(t) = \frac{p}{\lambda} \left(\frac{t}{\lambda} \right)^{p-1}$$

where: t is the time, p is the shape parameter, λ is the scale parameter.

The shape parameter p in the Weibull distribution controls the distribution's form (exponential when p=1; monotonic increasing or decreasing hazard for other values).

2. Data Preparation

Ensure that the dataset is correctly formatted with the variables Y (continuous), X (binary), M (continuous), and Zi (exogenous variables).

3. Stata Code for Generalized SEM

Below is the Stata code to fit the specified generalized SEM:

```
* Load the data
use your_dataset.dta, clear

* Define the model
gsem (X <- Z1 Z2 Z3, logit) ///
    (M <- X Z1 Z2 Z3, logit) ///
    (Y <- X M Z1 Z2 Z3, weibull)
```

Example:

```
**Class 1**
gsem (_t <- POLYPH NonWhite AGE SEX householdsize ztownsend SESres zLE8_TOTALSCOREinv
comorbid srhbr predclass1, family(weibull, failure(_d) ) link(log) nocapslatent) ///
(NonWhite -> POLYPH, family(binomial) link(logit)) ///
(AGE -> POLYPH, family(binomial) link(logit)) ///
(SEX -> POLYPH, family(binomial) link(logit)) ///
(householdsize -> POLYPH, family(binomial) link(logit)) ///
(ztownsend -> POLYPH, family(binomial) link(logit)) ///
```

```
(SESres -> POLYPH, family(binomial) link(logit)) ///
(zLE8_TOTALSCOREinv -> POLYPH, family(binomial) link(logit)) ///
(comorbid -> POLYPH, family(binomial) link(logit)) ///
(srhbr -> POLYPH, family(binomial) link(logit)) ///
(predclass1  -> POLYPH  , family(binomial) link(logit)) ///
if sample_final==1 & _trans2==1, nocapslatent method(ml)



* Output the results
estat ic, all
estat gof, stats(all)
```

4. Model Explanation

1. **Binary Exposure Model:** The exposure X is modeled through a logistic regression where X is predicted by the exogenous variables Zi .
2. **Mediator Model:** The binary mediator M is regressed on the exposure X and the exogenous variables Zi.
3. **Final Outcome Model:** The final outcome Y, assumed to follow a Weibull distribution, is modeled as a function of the exposure X, the mediator M, and the exogenous variables Zi.

5. Model Fit and Diagnostics

- The estat ic command is used to obtain information criteria (AIC and BIC) for model comparison.
- The estat gof command is used to obtain goodness-of-fit statistics for assessing the model fit.

6. Interpretation of Results

- The coefficients β1 and β2 indicate the direct effects of X and M on Y, respectively.
- The coefficients γ1 and δi provide insights into how the mediator and exposure are influenced by the exogenous variables.
- Assess the significance and magnitude of the coefficients to understand the relationships within the model.

Researchers can utilize generalized SEM (*gsem* command) in Stata to study intricate associations that involve a Weibull-distributed outcome, a binary exposure, a binary mediator, and many exogenous variables by adhering to these steps. In addition, indirect effects through M can be estimated and statistical significance assessed at a type I error rate of 0.05 assessed using non-linear combinations, namely the products of β_1 and γ_1, using *nlcom*. Standard error associated with this non-linear combination is estimated using the delta method. Nevertheless, in our present study, the direct effect of X on Y is of primary interest.

Main source: Stata and R manuals and help

Other sources: (5, 6, 8, 9)

ONLINE SUPPLEMENTARY MATERIALS 3: LITERATURE REVIEW ON SELECT COMMONLY USED MEDICATIONS IN RELATION TO NEURODEGENERATIVE DISEASE AND MORTALITY

candesartan_cilexetil

Candesartan cilexetil is a drug often used for arterial hypertension, however, it has been shown to produce positive effects for dementia, and other chronic conditions (10). In rat models, Candesartan cilexetil also showed a positive effect in models of Parkinson's disease, protecting dopaminergic neurons involved in blocking endoplasmic reticulum stress by inhibiting ATF4-CHOP-Puma pathway activation (11). Candesartan cilexetil effect in treating chronic conditions has been shown as protective against cardiovascular death, reduced hospitalizations, and all-cause mortality, however, blood pressure, serum potassium, and creatinine levels should be monitored (12, 13).

doxazosin

Doxazosin is a medication used for the treatment of urinary tract symptoms (14); however, it has been considered a potentially inappropriate medication for older adults and is often prescribed (15). Although doxazosin is often prescribed, some evidence shows an effect on reducing dementia with Lewy bodies in men (16). Additionally, some evidence showed a potential risk reduction in developing Parkinson's disease and slowing motor symptoms (17, 18). One study investigating in-hospital mortality from COVID-19 revealed doxazosin relative risk reduction for death of 74% (odds ratio 0.23; 95% CI 0.03-0.94; $p = 0.028$) (19).

Insulin

Studies of insulin and cognitive function have pointed to resistance to insulin (20, 21, 22). Insulin resistance and cognition studies have suggested that resistance may be a feature of Alzheimer's disease and cognitive impairments (20). It has recently been noted that dysfunction of insulin signaling can influence brain function, therefore increasing the risk of Alzheimer 's-related biomarkers like an increased number of beta-amyloid plaques and tau tangles (21). Also, insulin signaling is involved with miR-193b-3p/PGC-1α pathway, which plays an anti-inflammatory role during the early stages of Parkinson's disease (23). Triglyceride-glucose index, a validated marker for insulin resistance, was shown that at higher levels, it was associated with an increased risk of all-cause mortality (24), and an increased risk of heart failure for both men and women (25).

lansoprazole

Lansoprazole has been shown in animal models to improve locomotor activity, reduce tau, and increase the extent of phosphorylated tau-positive areas (26). In human imaging studies, (^{18}F) (18)N-methyl lansoprazole brain retention was low in mild-cognitive impaired/Alzheimer's disease patients despite a high affinity for tau in vitro (27). Lansoprazole, at new dosage levels, may be appropriate for patients with dysphagia, especially for the elderly who are neurologically impaired, such as Parkinson's disease, and reduced mortality (28). Additionally, lansoprazole appeared as a binding site for all fibrils for surface plasmon resonance and immunofluorescence staining in the brain for pS129-αSyn positivity in Parkinson's disease patients (29).

lisinopril

lisinopril has an 18-year cumulative incidence rate of 31.4% in Alzheimer's disease; however, this rate was nearly identical to chlorthalidone (30.5%) and amlodipine (31.1%) (30). Early onset androgenetic alopecia among men showed lower efficacy with lisinopril and other drugs for dyslipidemia, prediabetes, or hypertension; additionally, there is an association between early-onset androgenetic alopecia and Parkinson's disease resulting in decreased fertility (31). Lisinopril showed in a propensity score-matched cohort study that 52.4% of patients had died from the prescribed medication; however, it was effective in treating heart failure with reduced ejection fraction and had similar mortality rates with other prescribed medication (e.g., enalapril) (32).

Multivitamins

Supplements like multivitamins have inconclusive evidence being beneficial or harmful to cognitive outcomes, like Alzheimer-type dementia and Parkinson's disease (33, 34). Multivitamins use was commonly used for indications other than Parkinson's disease (34). Multivitamin supplements did not show as a protective factor against chronic conditions or death (35, 36).

Omega3

Improvement of cognitive function was associated with increased baseline and increment of omega-3 index (37), and non-docosahexaenoic acid omega-3 may be have positive effects (38). omega-3 polyunsaturated fatty acids show evidence of improving Parkinson's disease as well (39). Omega-3 polyunsaturated fatty acids have shown positive effects on locomotory alterations in parkinsonism (40). Circulating omega-3 polyunsaturated fatty acids showed a strong inverse association with all-cause cancer and cardiovascular disease mortality (41).

Perindopril

Perindopril has been documented to improve neurodegenerative disorders like dementia, Alzheimer's Disease, and Parkinson's disease (42). Perindopril additionally was shown to manage motor fluctuations and dyskinesia in Parkinson's disease (43). In animal models, perindopril showed protective effects against 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine-induced striatal dopamine and DOPAC depletion and mitigated severity of L-3, 4-dihydroxyphenylalanine induced dyskinesia in Parkinson's disease (44, 45). In a large study using private health insurance claims, the risk-adjusted all-cause mortality rate was lower with perindopril compared to enalapril but not losartan (common renin-angiotensin-aldosterone system inhibitors) (46).

Ramipril

Ramipril treatment has been documented to improve neurodegenerative disorders like dementia, Alzheimer's Disease, and Parkinson's disease (42). However, in one study, cognitive impairment occurred in 8% of patients allocated ramipril or given in a combination treatment, and cognitive decline was at 17% in patients allocated ramipril or given in a combination treatment (47). Despite this, ramipril does show reduced cardiovascular and cerebral risk (48), along with decreasing risk for all-cause mortality, cardiovascular mortality, and first hospitalization (32, 49).

Vitamin C

Vitamin C at increased levels of intake was associated with improved executive functioning (50). Those with Alzheimer's disease had significantly higher prevalence rates of vitamin C than those without cognitive impairments (51). Additionally, vitamin C (ascorbate) was positively associated with cognitive

function in Parkinson's disease (52). Levodopa, a common drug for somatic management of Parkinson's disease, showed improved absorption with vitamin C intake (53). However, vitamin C intake did show some associations with breast cancer and kidney stones, but the benefits of vitamin C intake (e.g., positive respiratory, neurological, ophthalmologic, musculoskeletal, renal, and dental outcomes) outweigh the potential risks (54).

Glucosamine

Habitual glucosamine supplement intake showed a lower risk of dementia, with potential causal associations refarming risk reduction (55, 56). Additionally, O-linked N-acetyl-glucosamine showed that at increased levels may slow synucleinopathies, including Parkinson's disease; but, may be detrimental to neurons and increase α-synuclein accumulation (57, 58). Habitual glucosamine supplement intake was shown to lower mortality for all causes, cancer, cardiovascular disease, respiratory and digestive diseases (59).

cod liver oil

Cod liver oil was associated with increased 25-hydroxy-vitamin D levels, and several studies suggested older adults cognitively impaired have lower 25-hydroxy-vitamin D levels (60). Cod liver oil is a common medication used for other indications other than Parkinson's disease (34). Vitamin D3, found naturally in cod liver oil, should be given to those with vitamin D deficiency, especially those with a history of falls, nontraumatic fractures, and osteoporosis (61). Additionally, coronary heart disease mortality showed as lower among omega-3 polyunsaturated fatty acids, mainly from cod liver oil (62).

primrose oil

Evening primrose oil showed improved motor performance, lowered inflammatory indicators, repaired dopamine quantities, and improved neuro histopathological lesions in rat models of Parkinson's disease (63). There have been studies that have shown evening primrose oil to be an anti-coagulant and anti-platelet with the potential to reduce cardiovascular morbidity and mortality in rat models (64). However, evening primrose oil is not well known if it is beneficial in high-risk women (65). There is currently insufficient information regarding the effects of evening primrose oil on cognition.

garlic

Garlic has been shown to have beneficial effects, such as protecting against amyloid-beta-induced neurotoxicity (66); however, at higher levels of consumption, reduced cognitive flexibility and speed processing(66), yet longitudinally such decline was not found (66). In a review of Persian medicine, garlic was found to have strong anti-Alzheimer's disease activities (67). Additionally, Persian Medicines such as garlic possess potent antioxidants and anti-inflammatory properties, target intra-plaque ferroptosis, lower lipid peroxidation and the risk of mortality, and Parkinson's disease-preventing properties (68, 69, 70).

chondroitin

Chondroitin sulfate proteoglycan-related enzymes show relationships to cognitive function. Removal of chondroitin sulfate proteoglycan negatively affects memantine on cognitive improvement in mice (71). Fucosylated chondroitin sulfate taken from sea cucumbers demonstrated positive effects in Parkinson's disease mouse models by reducing inflammation in the gut microbial dysbiosis (72). In a national sample of US adults, regular chondroitin intake was associated with reduced all-cause and cardiovascular disease mortality (73).

Supplementary Table 4. Latent classes of commonly used medications vs. transitions 2 and 3, as mediated through polypharmacy as defined by a cutoff of 5+ medications ($POLYPH^{5+}$): direct and indirect effects: UK Biobank 2006-2021

LC	Outcome	LC→$POLYPH^{5+}$			LC→Outcome			$POLYPH^{5+}$→Outcome		
		β	(SE)	P	β	(SE)	P	β	(SE)	P
1	**Healthy to Dementia**	**0.17**	**0.01**	**<0.001**	-0.02	0.04	0.64	**0.29**	**0.03**	**<0.001**
2	**Healthy to Dementia**	**0.81**	**0.01**	**<0.001**	-0.03	0.03	0.32	**0.29**	**0.03**	**<0.001**
3	**Healthy to Dementia**	**-0.38**	**0.03**	**<0.001**	+0.019	0.084	0.82	**0.29**	**0.03**	**<0.001**
4	**Healthy to Dementia**	**2.71**	**0.03**	**<0.001**	-0.14	0.08	0.08	**0.30**	**0.03**	**<0.001**
5	**Healthy to Dementia**	**0.24**	**0.02**	**<0.001**	-0.01	0.06	0.86	**0.29**	**0.03**	**<0.001**
6	**Healthy to Dementia**	**-3.00**	**0.02**	**<0.001**	-0.02	0.03	0.63	**0.28**	**0.03**	**<0.001**
7	**Healthy to Dementia**	**1.42**	**0.02**	**<0.001**	**-0.13**	**0.05**	**0.01**	**0.30**	**0.03**	**<0.001**
8	**Healthy to Dementia**	**0.76**	**0.08**	**<0.001**	0.08	0.21	0.70	**0.29**	**0.03**	**<0.001**
9	**Healthy to Dementia**	**1.21**	**0.02**	**<0.001**	**0.23**	**0.04**	**<0.001**	**0.26**	**0.03**	**<0.001**
1	**Healthy to Mortality**	**0.17**	**0.01**	**<0.001**	0.03	0.02	0.07	**0.27**	**0.01**	**<0.001**
2	**Healthy to Mortality**	**0.81**	**0.01**	**<0.001**	**-0.04**	**0.02**	**0.02**	**0.27**	**0.01**	**<0.001**

3	**Healthy to Mortality**	**-0.381**	**0.028**	**<0.001**	**-0.114**	**0.038**	**0.002**	**0.26**	**0.01**	**<0.001**
4	**Healthy to Mortality**	**2.71**	**0.03**	**<0.001**	**-0.22**	**0.04**	**<0.001**	**0.28**	**0.02**	**<0.001**
5	**Healthy to Mortality**	**0.24**	**0.02**	**<0.001**	**0.06**	**0.03**	**0.03**	**0.27**	**0.01**	**<0.001**
6	**Healthy to Mortality**	**-3.00**	**0.02**	**<0.001**	**0.08**	**0.01**	**<0.001**	**0.30**	**0.02**	**<0.001**
7	**Healthy to Mortality**	**1.42**	**0.02**	**<0.001**	**-0.21**	**0.02**	**<0.001**	**0.28**	**0.01**	**<0.001**
8	**Healthy to Mortality**	**0.76**	**0.08**	**<0.001**	**0.40**	**0.09**	**<0.001**	**0.26**	**0.01**	**<0.001**
9	**Healthy to Mortality**	**1.21**	**0.02**	**<0.001**	**0.07**	**0.02**	**<0.001**	**0.26**	**0.02**	**<0.001**

Abbreviations:

LC=Latent class; P=P-value; POLYPH^{5+}=Polypharmacy with 5+ medications cutoff; SE = Standard error; UK=United Kingdom.

Supplementary Figure 1. Participant Flowchart

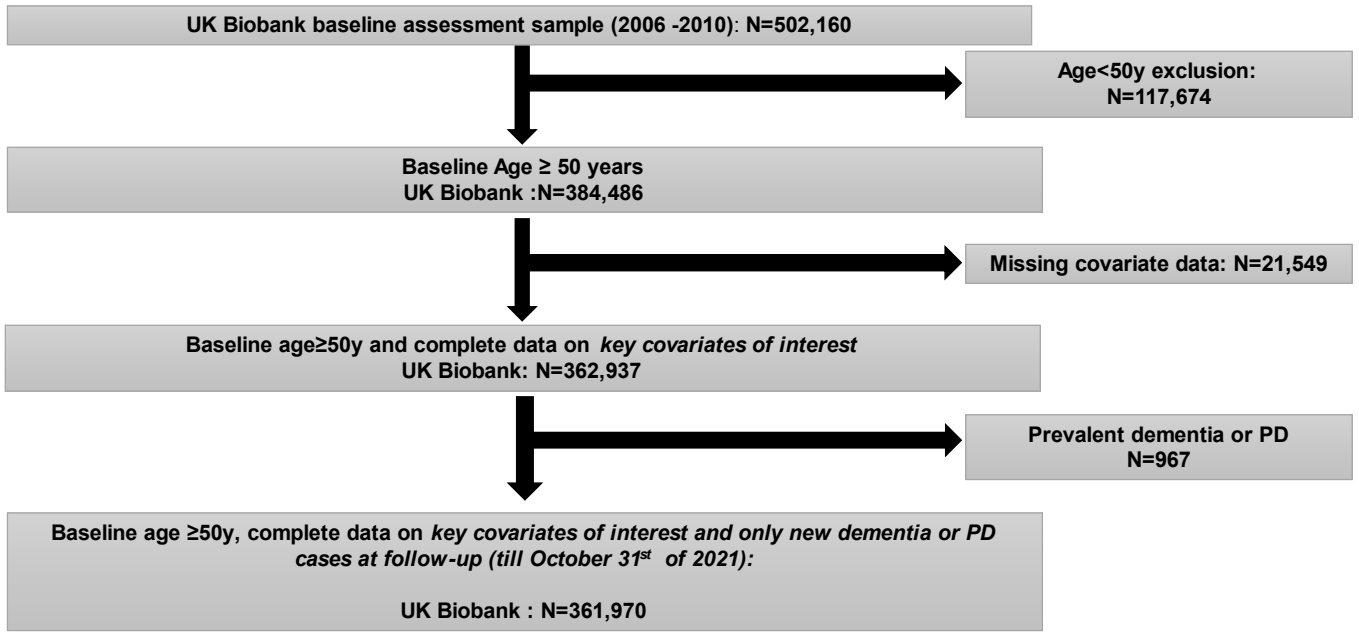
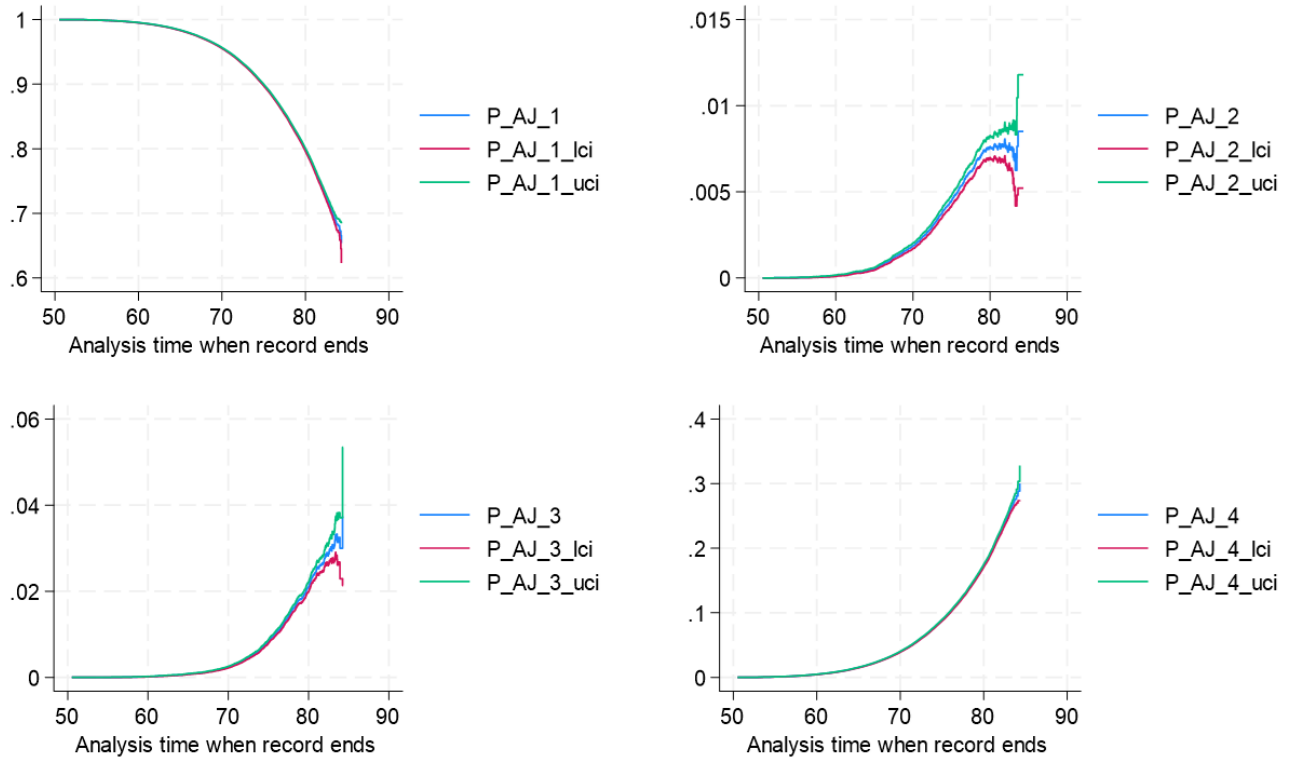


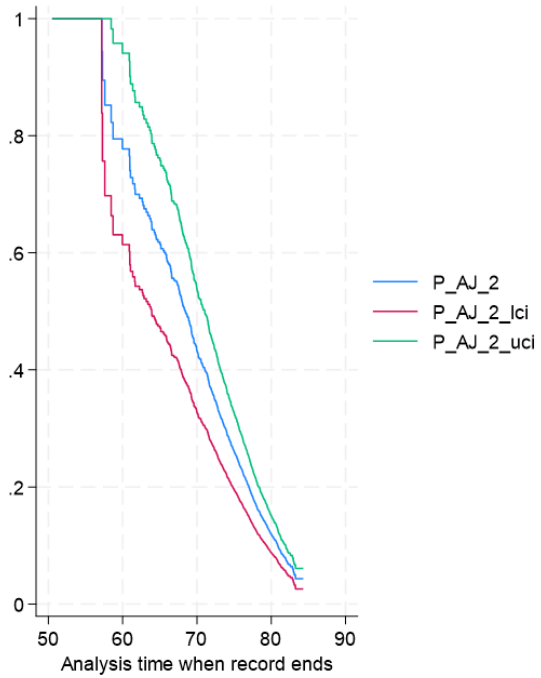
FIGURE S2. Probabilities of being in each of 4 states: UK Biobank 2006 -2021



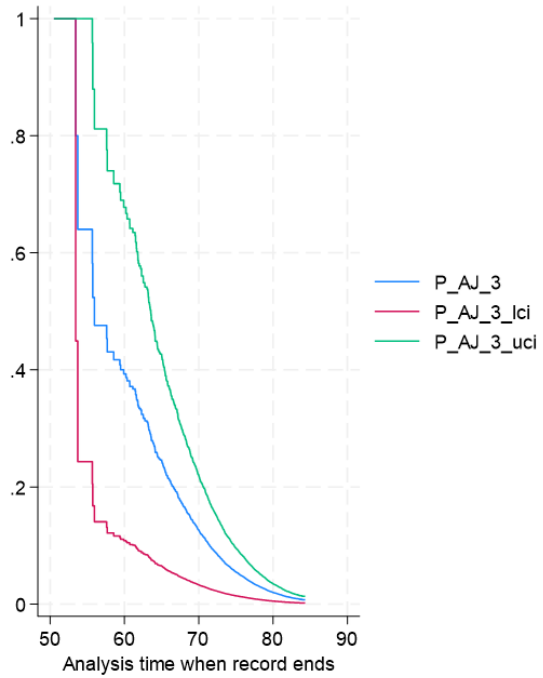
State 1: Healthy, State 2: PD, State 3: Dementia, State 4: Death

FIGURE S3. Transition probabilities from PD and Dementia across follow -up age: UK Biobank 2006-2021

(A) Transitions from PD



(B) Transitions from Dementia



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