Associations between Dementia Diagnosis and Hyperpolypharmacy: Jointly accounting for Dropout and Death

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Disclosure

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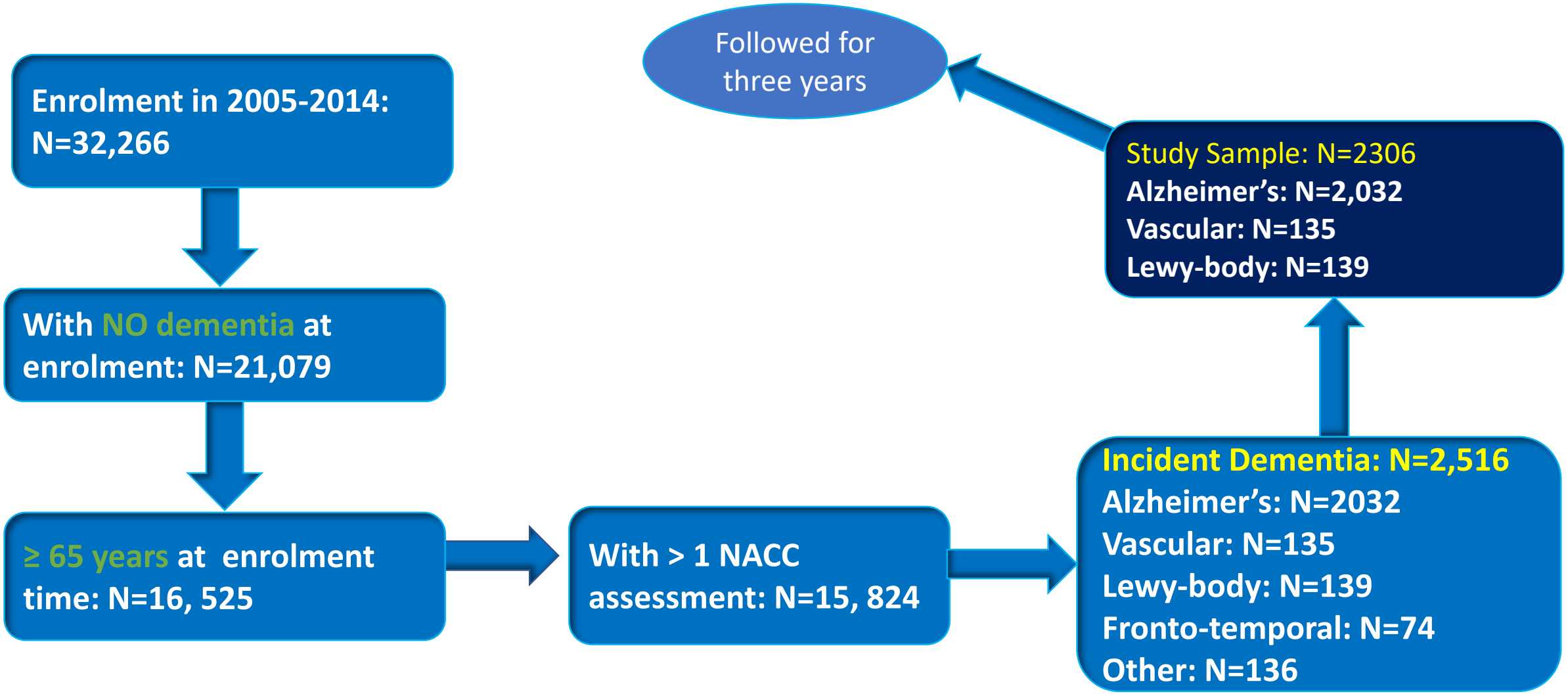
Introduction

- Longitudinal studies of older adults are characterized by high dropout rates, multimorbid conditions and multiple medication use especially proximal to death.
- We studied the association between multiple medication use and incident dementia diagnoses including Alzheimer's disease (AD), Vascular dementia (VD), and Lewy-body dementia (LBD), simultaneously accounting for dropout.
- Those with severe illness are more likely to die/drop out than those with less severe illness (non-ignorable missingness)
- Ignoring missingness may lead to biased estimates

NACC Analytic Sample



Study objective

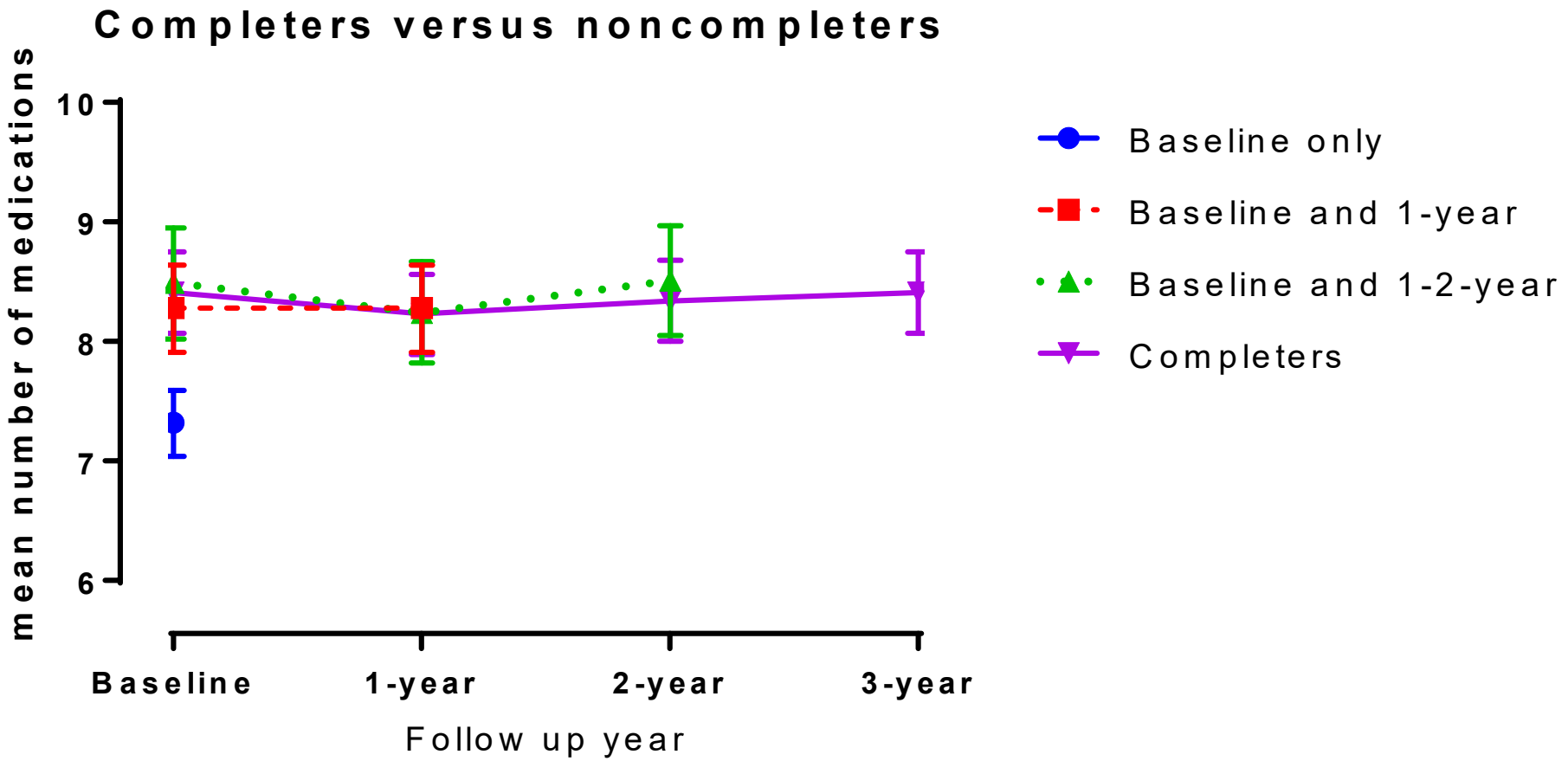
- Objective: to demonstrate how to account for dropout due to death and other reasons by studying the longitudinal association between medication use and incident diagnosis of Alzheimer's disease (AD), vascular dementia (VD), and Lewy-body dementia (LBD)

- Exposures:- Types of Dementia:
  - Alzheimer's disease
  - Vascular dementia
  - Lewy-Body dementia

Study variables

- Outcomes:-Medication use:
  - Hyper-polypharmacy (10 or more medications at visit time)
- Covariates:-
  - Sociodemographic
    - age, gender, race
  - Health characteristics
    - Myocardial infarction, atrial fibrillation, angioplasty, coronary artery bypass graft surgery, pace maker, congestive heart failure, other cardiovascular disease
    - Diabetes (type 1 or type 2), Depression
    - Psychiatric disorders

Completers versus partial completers



Summary of active, lost to follow-up and death

		Baseline	1-year	2-years	3-years
		N (%)	N (%)	N (%)	N (%)
Alzheimer's	Active†	2032 (100)	1529 (75.3)	890 (43.8)	572 (28.2)
	Cumulative Lost ‡		326 (16.1)	489 (24.1)	573 (28.2)
	Cumulative Deaths‡		176 (8.7)	297 (14.6)	382 (18.8)
	Cumulative Censoring‡			355 (17.4)	504 (24.8)
Vascular	Active†	135 (100)	83 (61.5)	39 (28.9)	25 (18.5)
	Cumulative Lost ‡		14 (10.4)	18 (13.3)	22 (16.3)
	Cumulative Deaths‡		38 (28.2)	55 (40.7)	60 (44.4)
	Cumulative Censoring‡			23 (17.4)	28 (20.1)
Lewy-Body	Active†	139 (100)	103 (74.1)	56 (40.3)	31 (22.3)
	Cumulative Lost ‡		15 (10.8)	29 (20.9)	35 (25.2)
	Cumulative Deaths‡		21 (15.1)	34 (24.5)	42 (30.3)
	Cumulative Censoring‡			20 (14.4)	31 (22.3)

† % reflects proportion of the visit 1-year active sample for each type of dementia

‡ % reflects cumulative proportion, defined as yearly cumulative frequency divided by baseline frequency for active sample for each type of dementia expressed as a percentage

‡ censoring refers to the number of participants who were diagnosed with dementia in 2014 and were only able to contribute one year of data during this study period

Hyper-polypharmacy distribution by follow-up

Follow-up	Medication	AD	VD	LBD
Baseline	N	N=2032	N=135	N=139
	Hyperpolypharmacy, N (%)	506 (25.5)	46 (35.1)	49 (35.8)
1-year	N	N=1174	N=60	N=83
	Hyperpolypharmacy, N (%)	378 (32.8)	20 (36.4)	43 (53.1)
2-years	N	N=742	N=34	N=45
	Hyperpolypharmacy, N (%)	238 (33.01)	14 (43.8)	19 (43.2)
3-years	N	N=430	N=24	N=28
	Hyperpolypharmacy, N (%)	160 (38.2)	11 (45.8)	11 (39.3)

Methods

Separate model => models the odds of hyper-polypharmacy for VD and LBD relative to AD with a random intercept

(each person may start with a different probability of hyper-polypharmacy)

Separate -complete case (MCAR) probability of dropout does not depend upon the observed outcomes

Separate -whole cohort (MAR) probability of dropping out depends on the observed outcomes and covariates at some time before dropping out, but not on the unobserved outcomes during or after dropout

Joint shared parameter model

- An intuitive approach to model the association between dementia types and medication use, simultaneously accounting for dropout due to death and other factors.
- Models the odds of hyper-polypharmacy for VD and LBD relative to AD and probability of missingness jointly conditional on observed covariates (e.g., age) and unobserved shared random effects (e.g., disease severity).
- The shared random effects quantify the unobserved quantities that underlie a subject's probability to use multiple medications or to dropout.

Benefits of the Joint Model

- Handles informative dropout -> when the probability of dropout depends on the unobserved outcome at the time of dropout.
- Intermittent missing data patterns,
- Can be applied if participants do not follow the same follow-up schedule;
- Hyper-polypharmacy and a person's probability to dropout may be related through observed subject's characteristics, such as disease status, and through their unobserved characteristics.
- Hyper-polypharmacy and dropout are modeled jointly conditional on a subject's observed characteristics and unobserved shared random effects.

Results

Hyper-polypharmacy outcome in the joint model: Odds Ratio (95% CI)

Medication use	Dementia diagnosis	Separate mixed model-complete case	Separate mixed model-whole cohort	Joint shared parameter model
Hyper-polypharmacy (≥10 medications)	VD	0.98 (0.37, 2.62)	1.59 (0.89, 2.84)	1.57 (0.82, 2.99)
	LBD	2.19 (0.78, 6.15)	3.00 (1.66, 5.40) *	1.41 (0.76, 2.64)
	$\hat{\sigma}_u^2$			5.26 (3.94, 6.59) *

$\hat{\sigma}_u^2$ is variance of the shared random effect; * significant, P <0.05

Drop out outcome in the joint model: Odds Ratio (95% CI)

Medication use	Dementia diagnosis	Dropout outcome in the joint model
Hyper-polypharmacy (≥10 medications)	VD	2.46 (0.62, 9.72)
	LBD	1.59 (0.28, 8.99)
	$\hat{\lambda}$	1.62 (1.06, 2.16) *

$\hat{\lambda}$ is log OR of the shared random effect to drop out

Discussion

- Positive association of dementia diagnosis with the probability of dropout
- Positive estimate that quantifies the association between unobserved random effects and dropout (increased risk)
- Dropout related to a person's health, may lead to too optimistic conclusions if not modelled.
- Shared parameter model can be implemented in standard statistical software, such as NLMIXED procedure in SAS.

Conclusion

- Ensure maximum retention of study participants to minimize missing data.
- Reasons for missing data should be ascertained.
- Appropriate statistical methods should be used to handle informative missingness to reduce bias in the risk estimates of interest.

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