Antihypertensives, Statins, and Risk for Dementias in Elders

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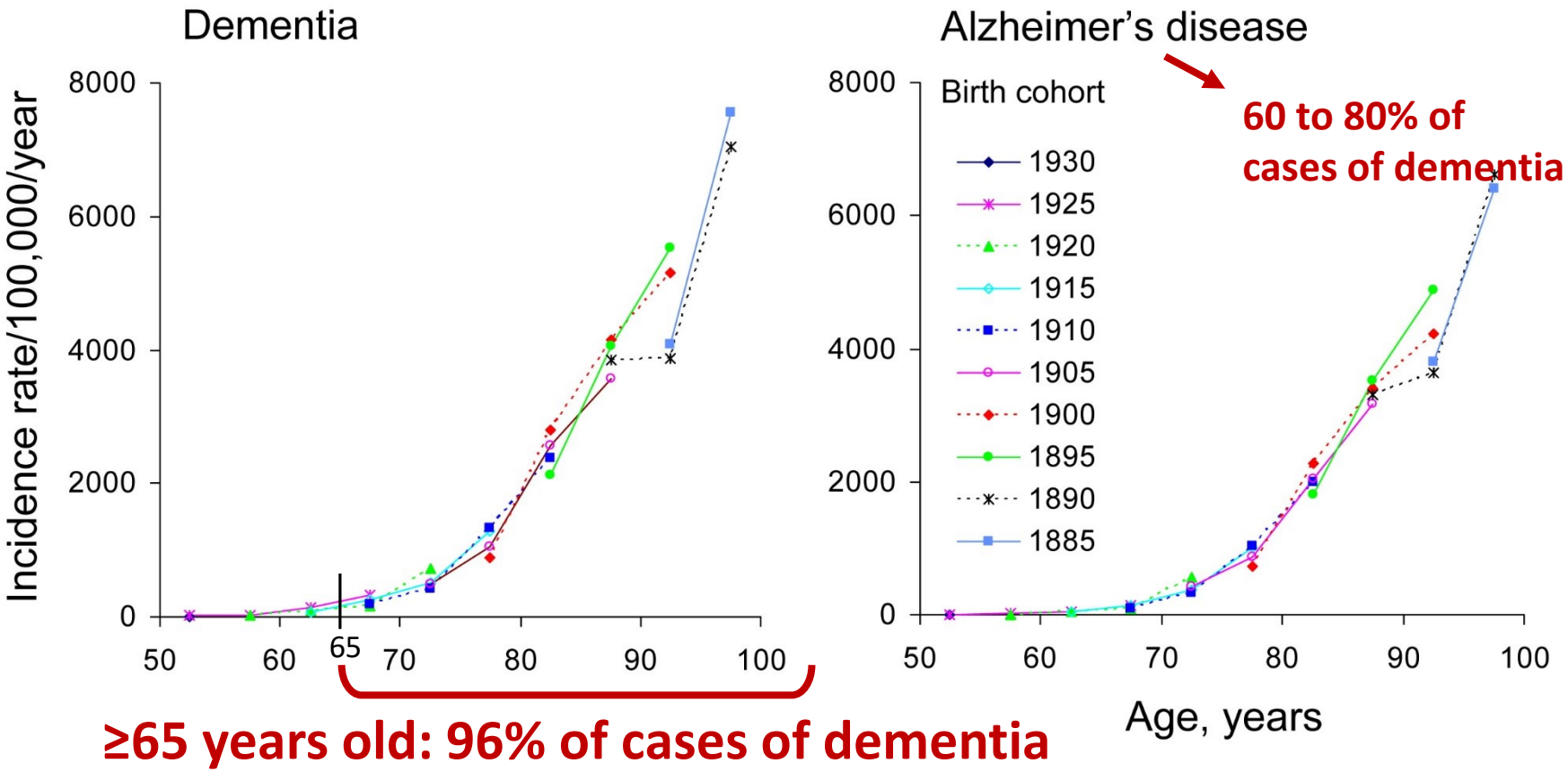
NLM 2017 Informatics Training Conference. June 6th, 2017.



Source: Rocca, W. A. et al. (2011). Trends in the incidence and prevalence of Alzheimer's disease, dementia, and cognitive impairment in the United States. *Alzheimer's & Dementia*, *7*(1), 80–93. doi:10.1016/j.jalz.2010.11.002

UpToDate, April 2017: *Prevention of dementia*

Antihypertensives:

- 👍 observational studies
- ? randomized trials

Statins:

- 👍 observational studies
- ? randomized trials

Challenges:

- Event rate
- Long follow-up
- Detailed follow-up
- *Proton pump inhibitors?*

Data source: CMS VRDC (Medicare claims)

Virtual Research Data Center, provided by the Centers for Medicare and Medicaid Services (CMS).

Our group has a 20% random cohort of all beneficiaries enrolled in Medicare Part D from 2006 to 2015.

Methods: beneficiary (patient) eligibility

a. Eligible for Medicare *due to* old age (65 years), no Medicare Part C (HMO), full Parts A, B and D.

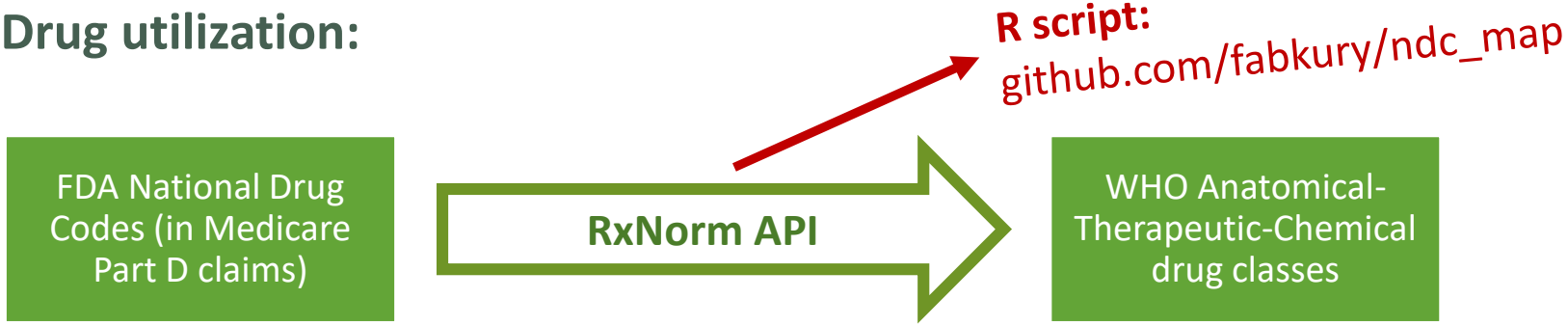
b. No prior history of dementia with 2-year claims wash-out.

c. At least 6 months of follow-up.

= 600,315 beneficiaries (from 20% cohort)

Methods: data preparation

Drug utilization:



ATC classes used:

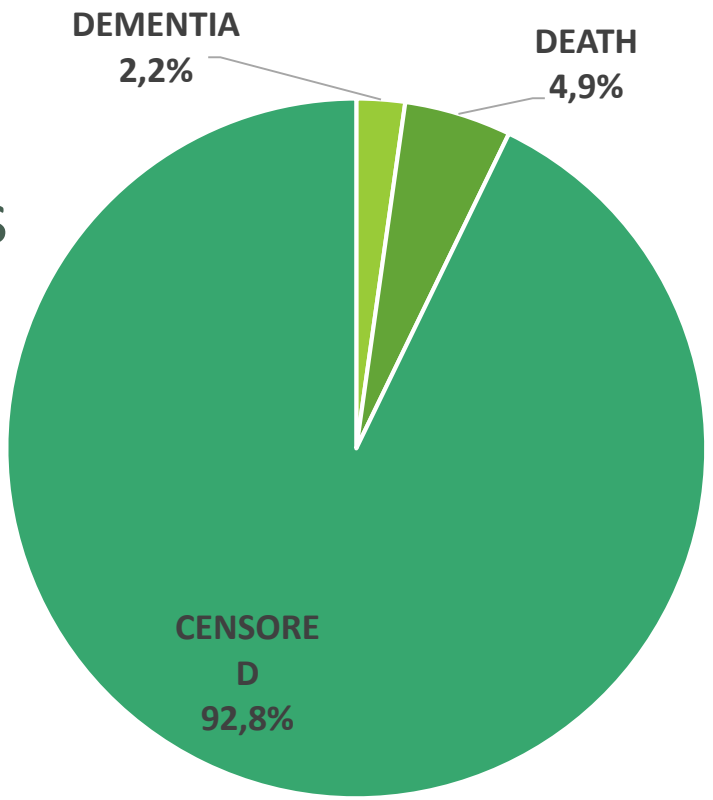
Statins	**C10AA, C10BA, C10BX**
Beta blockers	**C07**
Calcium channel blockers	**C08**
Diuretics	**C03**
Proton pump inhibitors	**A02BC**
Renin-angiotensin-aldosterone inhibitors	**C09**

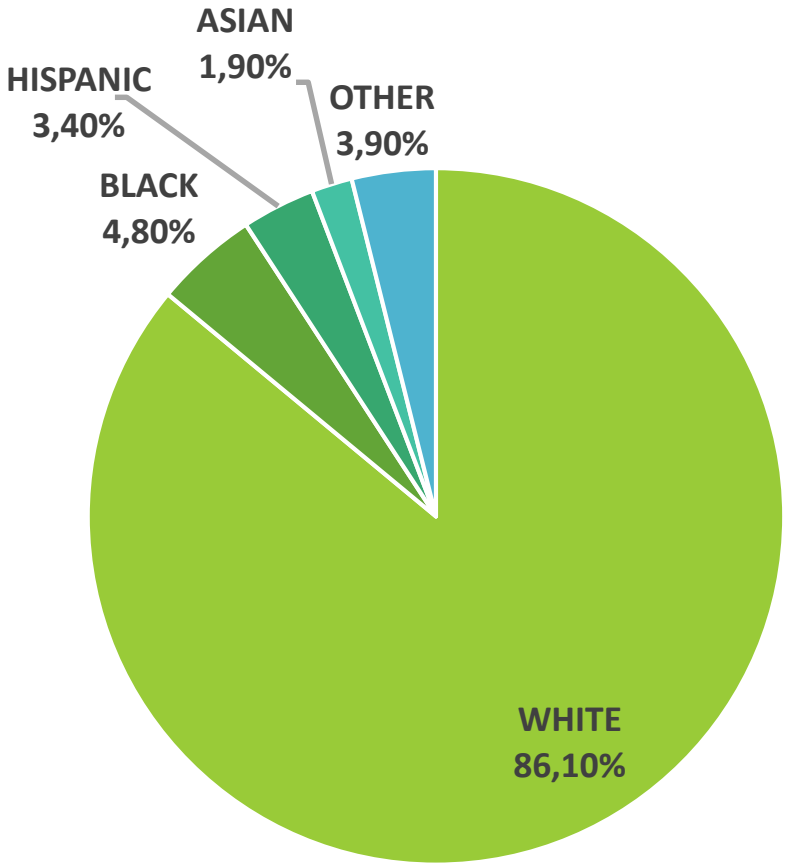
Methods: statistical analysis

- **Competing risk** regression with **time-varying covariates**.
  - Outcome: **dementia**; competing risk: **death**.
- Drug utilization: total **days** of drug use (not binary).
- Covariates:
  - Gender, ethnicity, residence in rural area } **Time-invariant**
  - Medicaid eligibility status
  - History of 57 chronic conditions:
    - myocardial infarction,
    - stroke,
    - several cancers,
    - diabetes,
    - several psychiatric disorders,
    - hyperlipidemia
    - hypertension
    - *...and many others*

} ***Time-variant***

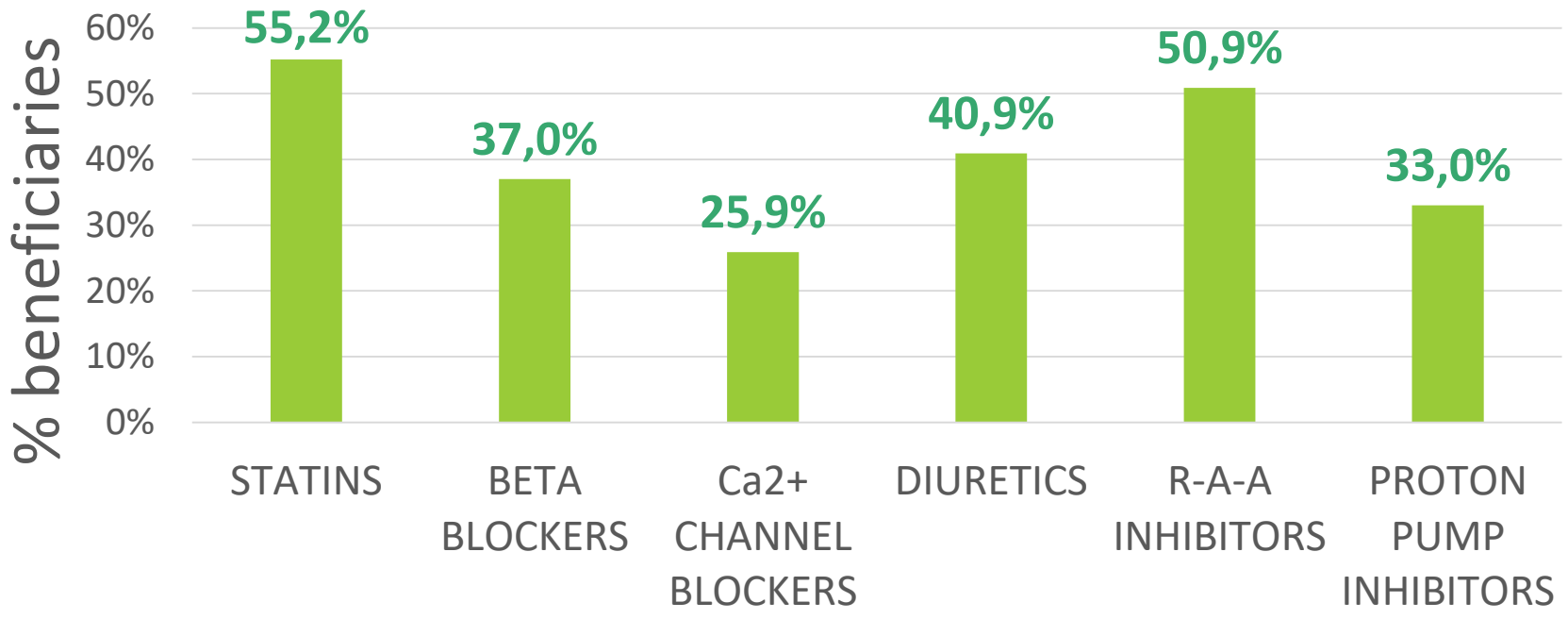
Results: cohort characteristics





BENEFICIARIES (PATIENTS)	**600,315**
AVG. YEARS OR FOLLOW-UP (SD)	4 (2.5)
FEMALE	60.2%
MEDICAID AND/OR L.I.S.	13.6%
RURAL AREA	24.3%

Results – cohort characteristics



Results – hazard ratio estimates (95% CI)

VARIABLE	REFERENCE	DEMENTIA	DEATH
STATINS	NO USE	*1.01 (0.95, 1.07)*	0.74 (0.70, 0.77)
BETA-BLOCKERS	NO USE	0.94 (0.89, 0.99)	0.83 (0.78, 0.87)
Ca^{2+}-CHANNEL BLOCKERS	NO USE	*0.98 (0.92, 1.04)*	*0.98 (0.94, 1.03)*
DIURETICS	NO USE	0.86 (0.81, 0.91)	*1.05 (0.99, 1.10)*
R-A-A INHIBITORS	NO USE	0.91 (0.86, 0.96)	0.73 (0.69, 0.76)
PROTON PUMP INHIBITOR	NO USE	*0.98 (0.92, 1.05)*	0.83 (0.78, 0.88)

Results – hazard ratio estimates (95% CI)

VARIABLE	REFERENCE	DEMENTIA	DEATH
ATRIAL FIBRILLATION	NEVER	1.11 (1.05, 1.17)	1.27 (1.21, 1.33)
HEART FAILURE	NEVER	1.15 (1.09, 1.21)	1.92 (1.84, 2.01)
ISCHEMIC HEART DISEASE	NEVER	1.16 (1.11, 1.21)	1.15 (1.11, 1.20)
DEPRESSION	NEVER	2.06 (1.93, 2.19)	1.08 (1.02, 1.15)
STROKE/T. ISCHEMIC ATTACK	NEVER	2.11 (2.00, 2.23)	1.37 (1.29, 1.46)
BREAST CANCER	NEVER	*0.97 (0.90, 1.05)*	1.62 (1.50, 1.75)
COLORECTAL CANCER	NEVER	*0.93 (0.82, 1.05)*	2.03 (1.86, 2.21)
LUNG CANCER	NEVER	0.85 (0.77, 0.95)	7.00 (6.61, 7.42)
PROSTATE CANCER	NEVER	*0.93 (0.78, 1.12)*	2.15 (1.80, 2.55)

Sensitivity analyses

		1	2	3
VARIABLE	**REFERENCE**	**DEMENTIA**		
STATINS	NO	1.01	1.03	1.01
BETA BLOCKERS	NO	1.34	1.25	0.94
CALCIUM CHANNEL BLOCKERS	NO	1.25	1.13	0.98
DIURETICS	NO	1.02	0.96	0.86
RAS INHIBITORS	NO	0.91	0.87	0.91
PROTON PUMP INHIBITOR	NO	1.75	1.47	0.98
FEMALE	MALE		0.96	0.91
BLACK	WHITE		1.29	1.31
HISPANIC	WHITE		1.08	1.19
ASIAN	WHITE		0.68	1.04
OTHER	WHITE		0.87	0.96
DUAL-ELIGIBLE	MEDICARE		4.83	2.86
LOW INCOME SUBSIDY	MEDICARE		2.33	1.95
LIVING IN RURAL AREA	NO		0.89	0.98

***Red: non-significant at 95% confidence level.**

Discussion, 1 of 2

2,4 million beneficiary-years

Billing (claims) data allowed for the largest study so far, as well as extensive + comprehensive follow-up.

VARIABLE	REFERENCE	DEMENTIA
STATINS	NO USE	***1.01 (0.95, 1.07)***
PROTON PUMP INHIBITOR	NO USE	***0.98 (0.92, 1.05)***

Discussion 2 of 2

Confounding effect of death rates cannot be ignored.

VARIABLE	REFERENCE	DEMENTIA	DEATH
BREAST CANCER	NEVER	*0.97 (0.90, 1.05)*	1.62 (1.50, 1.75)
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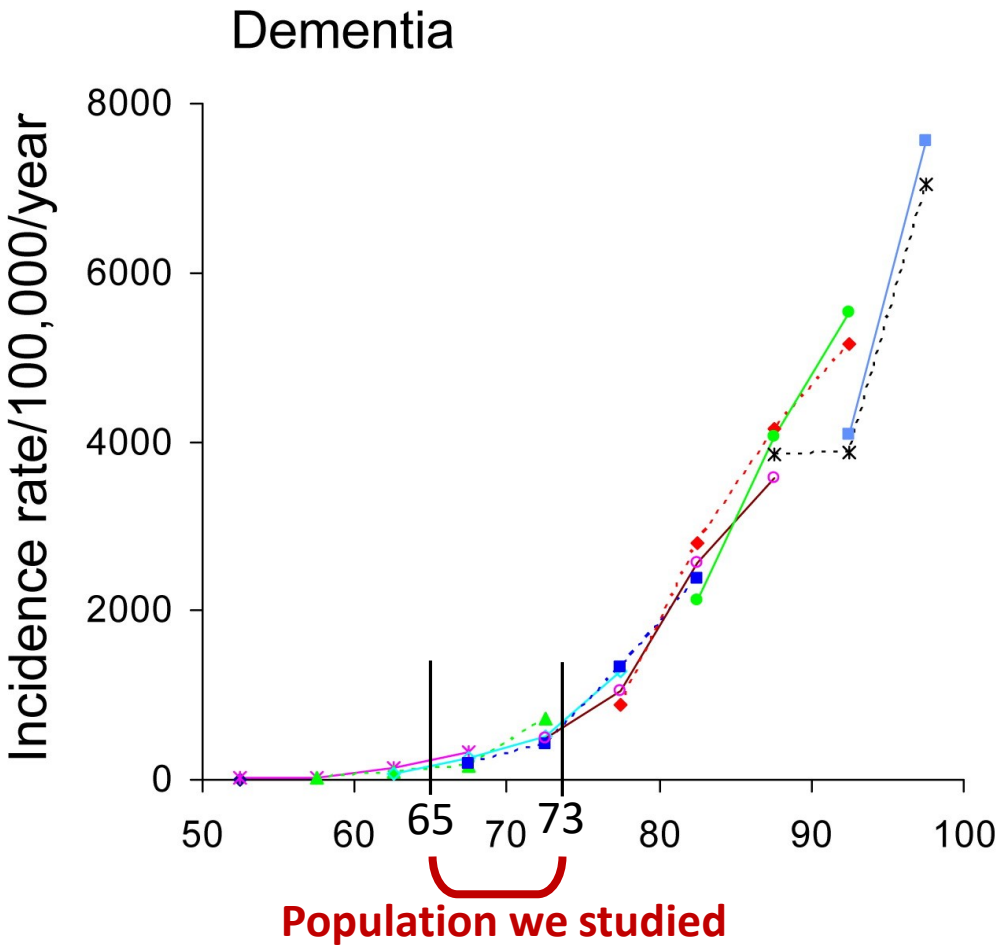
Limitations



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Sensitivity and specificity of medicare claims to identify dementia and Alzheimer's disease[a]

1a. Dementia[b]

		ADAMS					
		Yes	**No**	**Total**			
Medicare claims						**Raw %**	**Weighted %**
	Yes	235	68	303	Sensitivity	85.5%	84.8%
					Specificity	85.9%	89.2%
	No	40	415	455	Positive predictive value	77.6%	56.0%
					Negative predictive value	91.2%	97.3%
	Total	275	483	758			

1b. Alzheimer's disease[c]

		ADAMS					
		Yes	No	Total			
Medicare claims							
	Yes	126	49	175	Sensitivity	61.5%	64.2%
					Specificity	91.1%	95.2%
	No	79	504	583	Positive predictive value	72.0%	58.3%
					Negative predictive value	86.4%	96.2%
	Total	205	553	758			

https://ccwdata.org/web/guest/condition-categories

ADAMS = Aging, Demographics and Memory Study.

[a] All types of Medicare claims records were used: inpatient, outpatient; part B physician supplier file; home health; Skilled Nursing Facility (SNF); hospice, and durable medical equipment. A code corresponding to Alzheimer's disease or more generally dementia could appear in either the primary or secondary diagnosis position of a claim.

[b] Dementia was noted by a series of codes used in past work, including ICD-9-CM code 331.0, Alzheimer's disease.

[c] Alzheimer's disease was noted by the presence of ICD-9-CM code 331.0.

Source: Taylor Jr. et al. J Alzheimers Dis. 2009; 17(4): 807–815. doi: 10.3233/JAD-2009-1099

Conclusion

Unable to identify protective association of **statins**, and adverse association of **proton pump inhibitors.**

Antihypertensives seem to be protective... but perhaps not via parallel machanisms of action of any particular drug class.

github.com/fabkury/rxad

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Thank you!