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Neuropsychiatric symptoms as predictors of MCI and dementia: Epidemiologic evidence

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Conflict of interest

- Dr Geda served as an advisory board member to Lundbeck in March of 2017.
- Dr Geda is funded by the European Union, NIH and the Edward and Lili foundation (Hague, the Netherlands)

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Outline

- Introduction: Neuropsychiatric symptoms (NPS), MCI and dementia
- Study 1: From normal aging to incident MCI as predicted by baseline NPS *(Geda et al. Am J Psychiatry. 2014)*
- Study 2: From MCI to incident dementia as predicted by baseline NPS *(Pink et al., Neurology. 2015)*
- NPS and neuroimaging biomarkers of pre-symptomatic AD

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Introduction: NPS, MCI and dementia

- Neuropsychiatric symptoms (NPS) are highly prevalent in patients with MCI *(Lyketsos, JAMA 2002; Geda, Arch Gen Psychiatry 2008)*
- Prevalence of NPS in MCI ranges from 35% - 85% *(Monastero, J Alzheimers Dis 2009; Review)*
- Most common NPS are apathy, depression, and irritability in both Cardiovascular Health Study *(Lyketsos, JAMA 2002)* and Mayo Clinic Study of Aging *(Geda, Arch Gen Psychiatry 2008)*

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Population-based indices of depression

Author	Study	Sample size/age	Prevalence/Frequency
Lyketsos et al., 2002	Cardiovascular Health Study	320 MCI, 362 dementia, ≥ 65 yrs	20.1% (MCI), 32.3% (dementia)
Geda et al., 2008	Mayo Clinic Study of Aging	329 MCI, 1640 CN, ≥ 70 yrs	27.0% (MCI), 11.4% (CN)
Lyketsos et al., 2000	Cache County Study	673 no dementia, 329 dementia, ≥ 65 yrs	7.0% (CN), 23.7% (dementia)
Steffens et al., 2000	Cache County Study	4559 no dementia, ≥ 65 yrs	Point prevalence: 5.3% Lifetime prevalence: 15.8%
Okura et al., 2010	Aging, Demographics & Memory Study	856, ≥ 71 yrs	12% (CN), 30% (CIND), 25% (dementia)
Chan et al., 2003	Memory and Medical Care Study, MD, USA	121 MCI, 333 dementia	15.7% (MCI), 21.9% (dementia)
Luppa et al., 2011	Leipzig Study of the Aged, GER	1006, ≥ 75 yrs	38.2%

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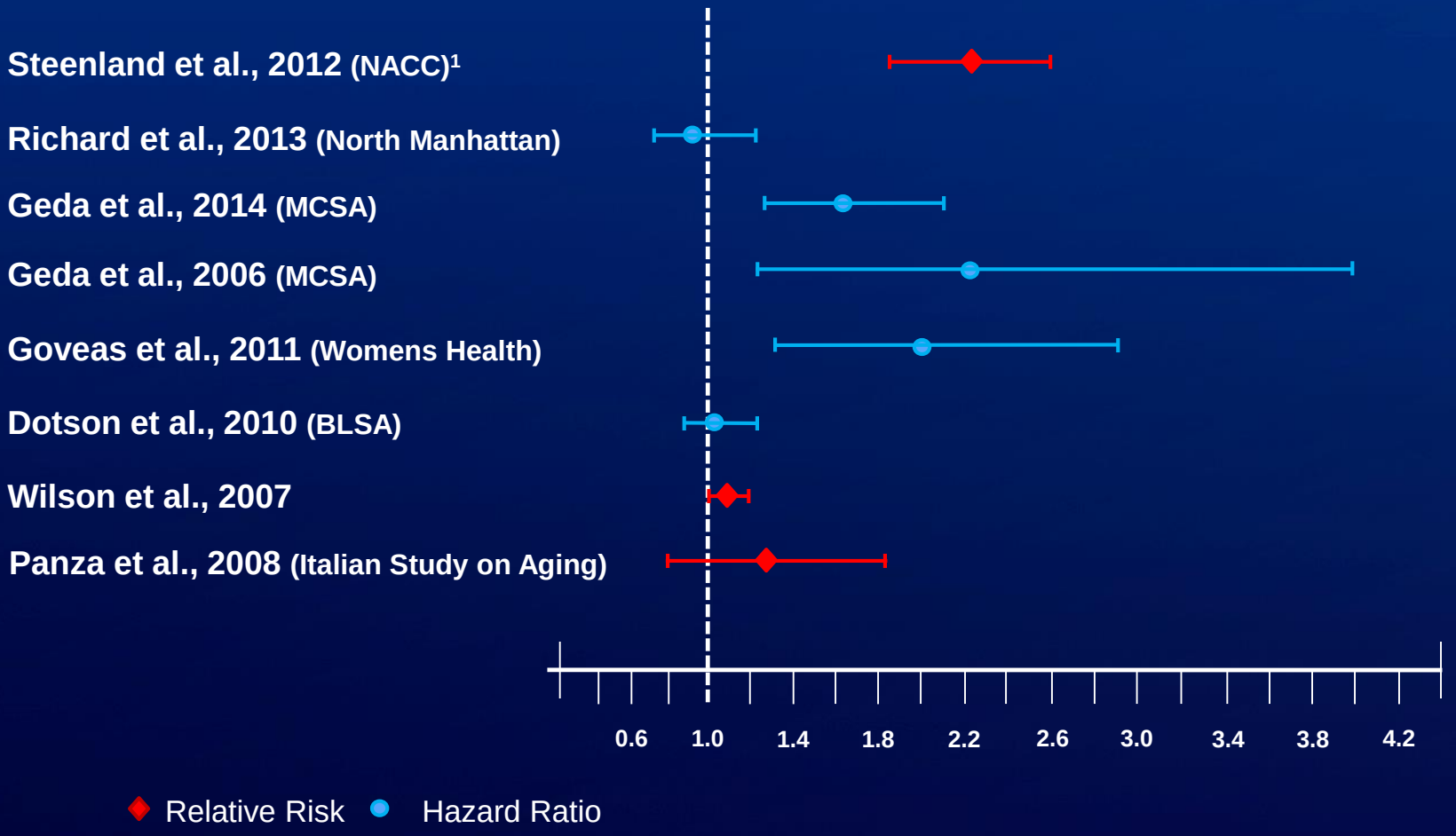
Depression predicting CN to iMCI



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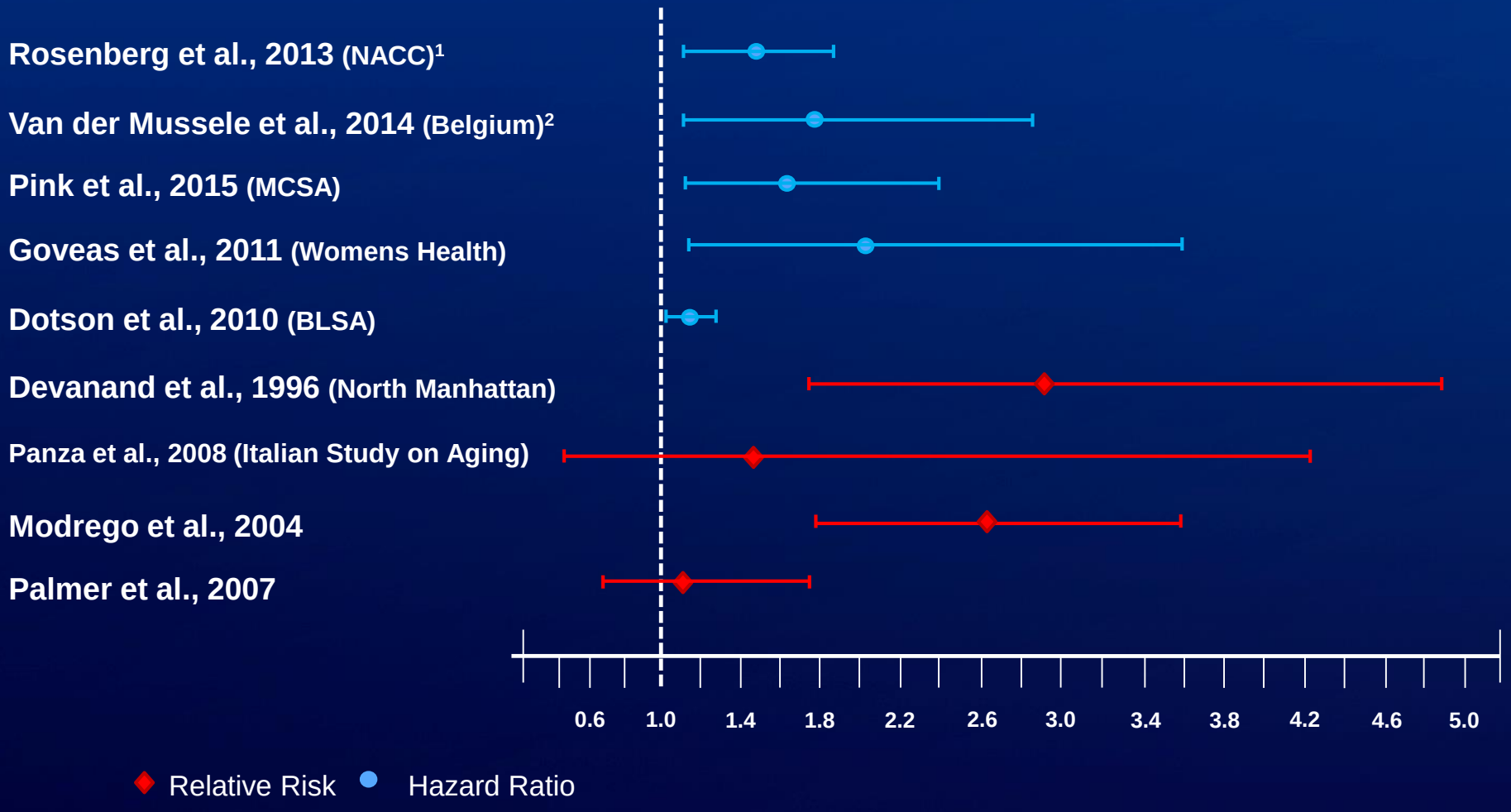
Depression predicting MCI to iDementia/ iAD



[1] GDS > 0; [2] GDS-30

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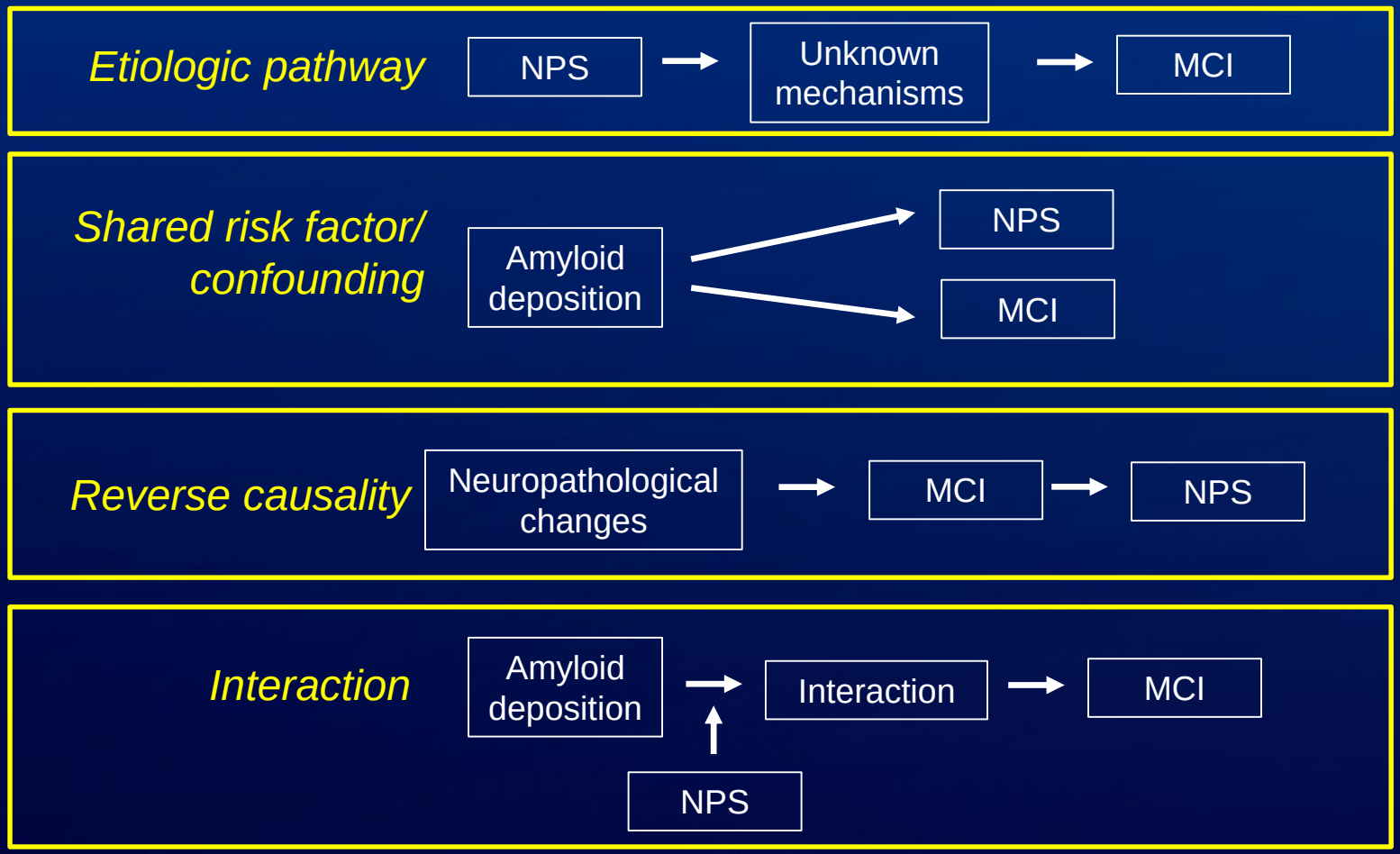
Potential mechanisms linking NPS with MCI/ dementia



Adapted from Geda et al., Alzheimers Dement. 2013 Sep;9(5):602-8.

Study Setting

Prospective cohort study derived from the population-based Mayo Clinic Study of Aging in Olmsted County, MN

PI: Dr. Ronald C. Petersen ***(Roberts, Geda et al., 2008)***

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Methods

- Classification of normal cognitive aging, MCI, and dementia
  - adjudicated by an expert consensus panel
  - based on published criteria
  - after reviewing neurologic, cognitive, and other pertinent data
- Hazard ratios (HR) and 95% confidence intervals (95% CI) were computed using Cox proportional hazards model, with age as a time scale
- NPS at baseline : measured by Neuropsychiatric Inventory Questionnaire (NPI-Q)

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Study 1: Objective

- Prospective cohort study to estimate the risk of incident mild cognitive impairment (MCI) in cognitively normal elderly (aged ≥70 years) individuals, with or without neuropsychiatric symptoms (NPS) at baseline

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Design: Prospective cohort study

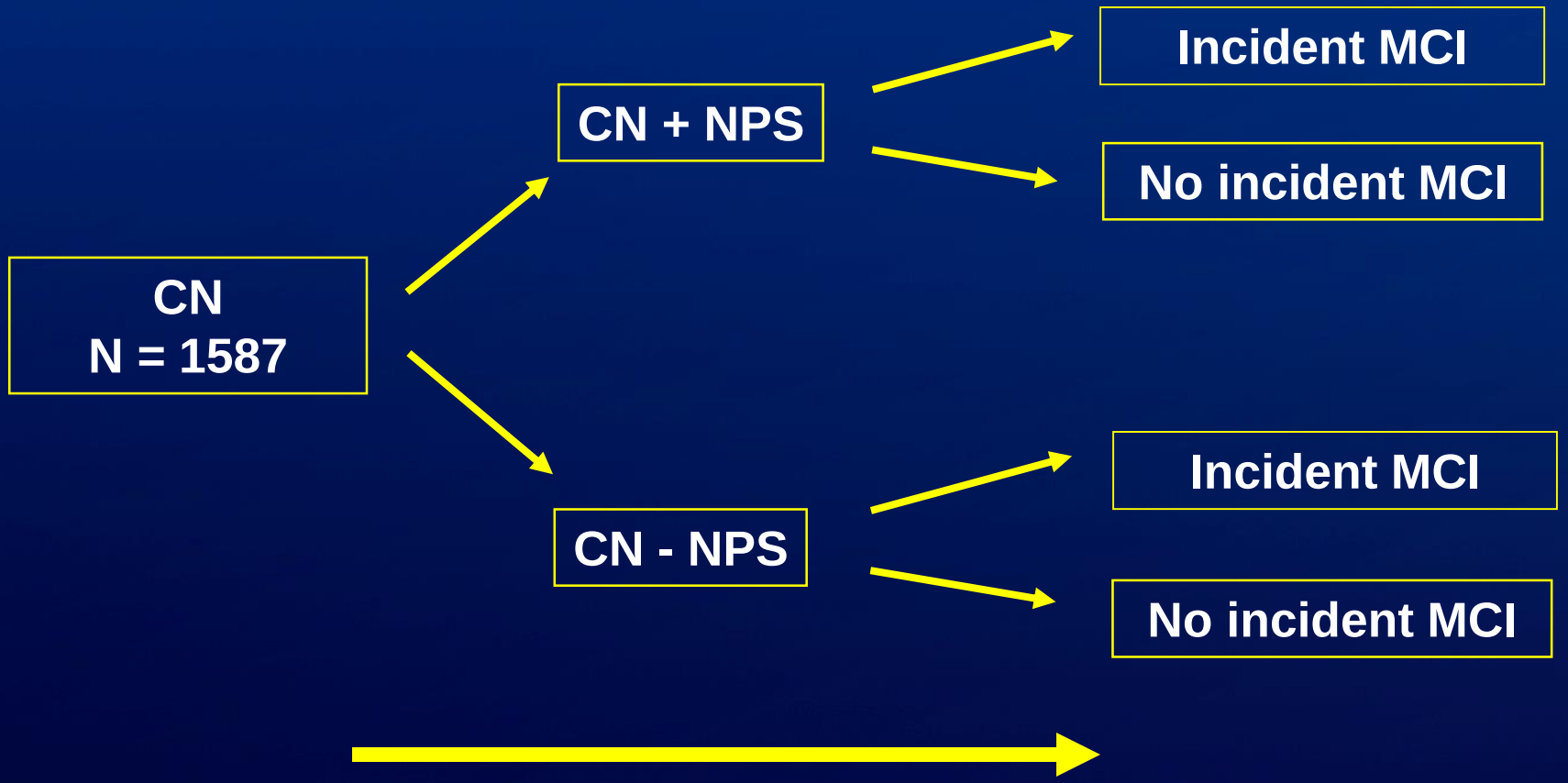

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TABLE 3. Risk of Incident Mild Cognitive Impairment by Baseline Nonpsychotic Neuropsychiatric Symptoms

	Risk Adjusted for Age (Time Scale), Sex, and Education			Risk Additionally Adjusted for Medical Comorbidity		
Psychiatric Symptom	Hazard Ratio	95% CI	p	Hazard Ratio	95% CI	p
Total mild cognitive impairment						
Depression	1.68	1.27–2.22	<0.001	1.63	1.23–2.16	<0.001
Apathy	2.46	1.63–3.70	<0.001	2.26	1.49–3.41	<0.001
Anxiety	1.91	1.31–2.78	<0.001	1.87	1.28–2.73	0.001
Agitation	3.13	1.94–5.05	<0.001	3.06	1.89–4.93	<0.001
Irritability	1.85	1.32–2.60	<0.001	1.84	1.31–2.58	<0.001
Appetite/eating	1.44	0.96–2.17	0.08	1.34	0.89–2.02	0.16
Motor disturbance	1.63	0.52–5.11	0.40	1.60	0.51–5.00	0.42
Nighttime behaviors[a]	1.48	1.05–2.08	0.03	1.46	1.03–2.06	0.03
Amnestic mild cognitive impairment						
Depression	1.75	1.23–2.48	0.002	1.74	1.22–2.47	0.002
Apathy	1.98	1.13–3.47	0.02	1.93	1.09–3.41	0.02
Anxiety	1.65	0.99–2.76	0.05	1.64	0.98–2.74	0.06
Agitation	2.18	1.07–4.44	0.03	2.16	1.06–4.41	0.03
Irritability	1.69	1.09–2.64	0.02	1.69	1.08–2.63	0.02
Appetite/eating	1.09	0.61–1.95	0.78	1.06	0.59–1.91	0.85
Motor disturbance	0.84	0.12–6.01	0.86	0.84	0.12–5.97	0.86
Nighttime behaviors[a]	1.44	0.93–2.24	0.11	1.44	0.93–2.25	0.10
Nonamnestic mild cognitive impairment						
Depression	1.26	0.68–2.31	0.46	1.18	0.64–2.16	0.60
Apathy	3.81	1.97–7.38	<0.001	3.19	1.62–6.26	<0.001
Anxiety	2.84	1.50–5.35	0.001	2.74	1.45–5.16	0.002
Agitation	5.14	2.46–10.7	<0.001	4.92	2.36–10.3	<0.001
Irritability	2.18	1.18–4.02	0.01	2.18	1.18–4.03	0.01
Appetite/eating	1.52	0.70–3.30	0.29	1.31	0.60–2.85	0.50
Motor disturbance	4.12	1.00–16.9	<0.05	3.89	0.94–16.0	0.06
Nighttime behaviors[a]	2.11	1.15–3.88	0.02	2.04	1.11–3.76	0.02

[a] Nighttime behaviors assessment data were not available for 271 participants (the informant was unable to assess).

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TABLE 4. Risk of Incident Mild Cognitive Impairment by Baseline Psychotic Symptoms and Other Emotional Behaviors

	Risk Adjusted for Age (Time Scale), Sex, and Education			Risk Additionally Adjusted for Medical Comorbidity		
Psychiatric Symptom	Hazard Ratio	95% CI	p	Hazard Ratio	95% CI	p
Total mild cognitive impairment						
Disinhibition	2.60	1.42–4.75	0.002	2.59	1.42–4.73	0.002
Euphoria	5.07	2.23–11.5	<0.001	5.10	2.24–11.6	<0.001
Delusions	0.60	0.08–4.27	0.61	0.55	0.08–3.95	0.55
Hallucinations	1.57	0.39–6.37	0.52	1.48	0.37–5.99	0.58
Amnestic mild cognitive impairment						
Disinhibition	1.49	0.55–4.01	0.43	1.48	0.55–4.00	0.44
Euphoria	2.42	0.59–9.84	0.22	2.41	0.59–9.83	0.22
Delusions	1.02	0.14–7.34	0.98	1.00	0.14–7.15	1.00
Hallucinations	1.32	0.18–9.52	0.78	1.30	0.18–9.34	0.80
Nonamnestic mild cognitive impairment						
Disinhibition	5.22	2.26–12.0	<0.001	5.18	2.24–12.0	<0.001
Euphoria	10.7	3.27–35.1	<0.001	11.3	3.44–37.2	<0.001
Delusions[a]			0.99			0.99
Hallucinations	3.10	0.42–22.7	0.27	2.76	0.38–20.3	0.32

[a] Values for hazard ratios and 95% confidence intervals were not applicable.

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Conclusion

- HR for hippocampal volume in predicting incident MCI is 1.8 (95% CI=1.4-2.20) (Kantarci et al., 2013)
- HR for apathy in predicting incident MCI is 2.26 (95% CI=1.49-3.41) and 3.06 for agitation (95% CI=1.89-4.93)
- Difference in strength of predicting incident MCI by biomarker compared to NPS cannot be attributed to methodological difference (both research took place in the context of MCSA)
- Risk of incident MCI by baseline NPS was as strong as or stronger than risk predicted by APOEε4, medical comorbidities, or demographic variables (e.g., low education)

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Study 2: Objective

- To investigate the population-based interaction between a biological variable (APOEε4), NPS, and the risk of incident dementia among subjects with prevalent MCI

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Design: Prospective cohort study

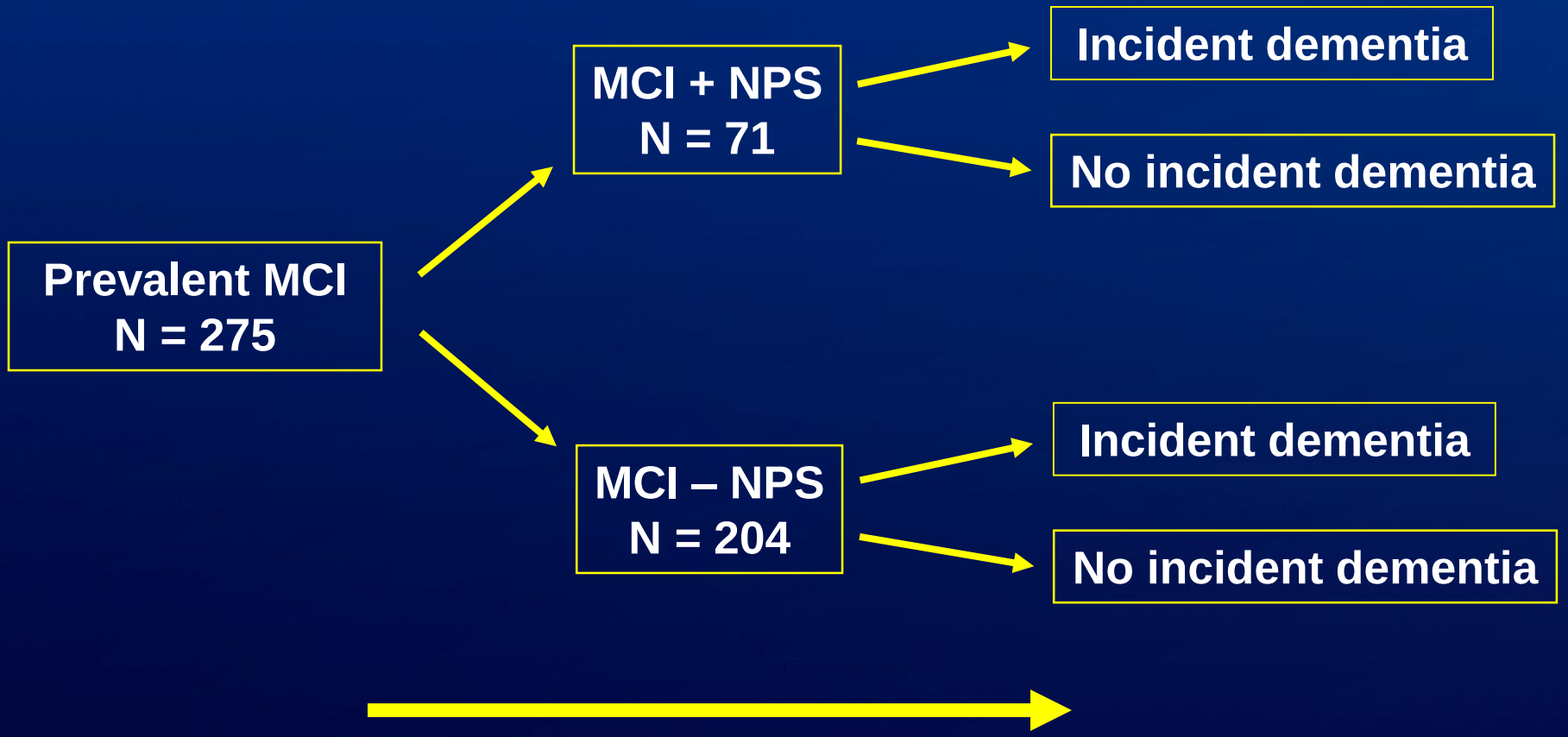

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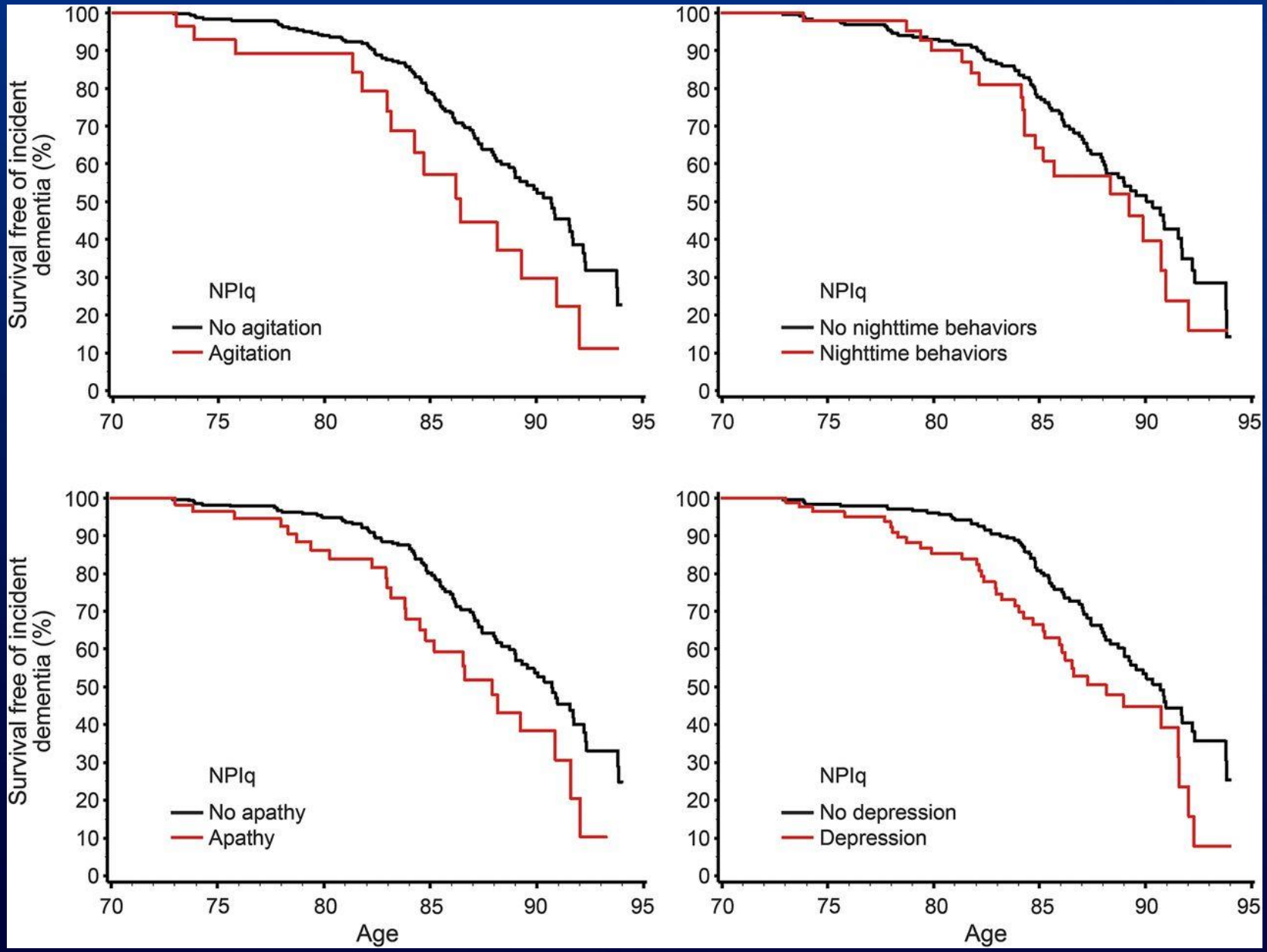
Table 2 Risk of incident dementia by neuropsychiatric symptoms[a]

Psychiatric symptom	HR (95% CI)[b]	*p* Value[b]
Depression	1.63 (1.10, 2.41)	0.015
Apathy	1.62 (1.03, 2.54)	0.037
Anxiety	0.93 (0.54, 1.61)	0.79
Agitation	1.97 (1.13, 3.42)	0.017
Irritability	1.00 (0.61, 1.67)	0.99
Appetite/eating	1.59 (0.86, 2.95)	0.14
Motor disturbance	0.78 (0.11, 5.71)	0.81
Nighttime behaviors	1.68 (1.02, 2.78)	0.042
Disinhibition	0.88 (0.32, 2.40)	0.80
Euphoria	3.06 (0.68, 13.7)	0.14
Delusions	1.43 (0.52, 3.96)	0.49
Hallucinations	NA	0.99

Abbreviations: CI = confidence interval; HR = hazard ratio; NA = not applicable.
[a] Bonferroni *p* value cutoff = 0.0042.
[b] Adjusted for age, sex, education, and medical comorbidity.


Survival free of incident dementia (%)
NPIq
No agitation
Agitation
NPIq
No nighttime behaviors
Nighttime behaviors
Survival free of incident dementia (%)
NPIq
No apathy
Apathy
NPIq
No depression
Depression
Age
Age

Interaction between NPS, APOEε4 and incident dementia

Sample or stratum	No. at risk	No. with dementia	Median time in study, y	HR (95% CI)[b]	p Value	Multiplicative interaction p value	Additive interaction p value
APOE4– DEP–	168	52	3.2	1.00 (ref. group)		0.29	<0.001
APOE4+ DEP–	78	24	2.9	1.02 (0.62, 1.66)	0.95		
APOE4– DEP+	53	22	3.1	1.39 (0.84, 2.31)	0.20		
APOE4+ DEP+	30	16	3.9	2.21 (1.24, 3.91)	0.007		
APOE4– APA–	185	59	3.0	1.00 (ref. group)		0.91	0.031
APOE4+ APA–	90	31	2.8	1.17 (0.76, 1.82)	0.48		
APOE4– APA+	36	15	4.0	1.55 (0.87, 2.76)	0.13		
APOE4+ APA+	18	9	4.0	1.93 (0.93, 3.98)	0.08		
APOE4– AGI–	201	64	3.2	1.00 (ref. group)		0.69	0.25
APOE4+ AGI–	101	36	2.9	1.24 (0.82, 1.87)	0.31		
APOE4– AGI+	20	10	3.0	2.07 (1.04, 4.11)	0.038		
APOE4+ AGI+	7	4	4.0	1.98 (0.71, 5.54)	0.19		
APOE4– BEV–	154	51	3.6	1.00 (ref. group)		0.35	0.44
APOE4+ BEV–	76	29	2.9	1.44 (0.90, 2.30)	0.13		
APOE4– BEV+	33	14	2.9	1.95 (1.06, 3.58)	0.031		
APOE4+ BEV+	12	5	2.7	1.62 (0.63, 4.16)	0.32		

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Conclusion

- NPS (depression, apathy, agitation) significantly predict progression from prevalent MCI to incident dementia
- Synergistic interaction between depression or apathy and APOE ε4 in further elevating the risk of incident dementia
- NPS may thus be useful clinical markers and clinicians may want to conduct a thorough evaluation looking for NPS
- If and when an NPS is identified then treatment may be warranted

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NPS and neuroimaging biomarkers of presymptomatic AD

Our team has reported cross-sectional associations between

- anxiety symptoms with reduced global cortical thickness and reduced thickness of the frontal and temporal cortex as measured by MRI *(Pink et al., 2016)*
- depressive and anxiety symptoms with an abnormal FDG-PET, and the point estimate is even higher for APOE ε4 carriers *(Krell-Roesch et al., 2016)*
- depression and anxiety with an abnormal PiB-PET *(Krell-Roesch et al., in press)*

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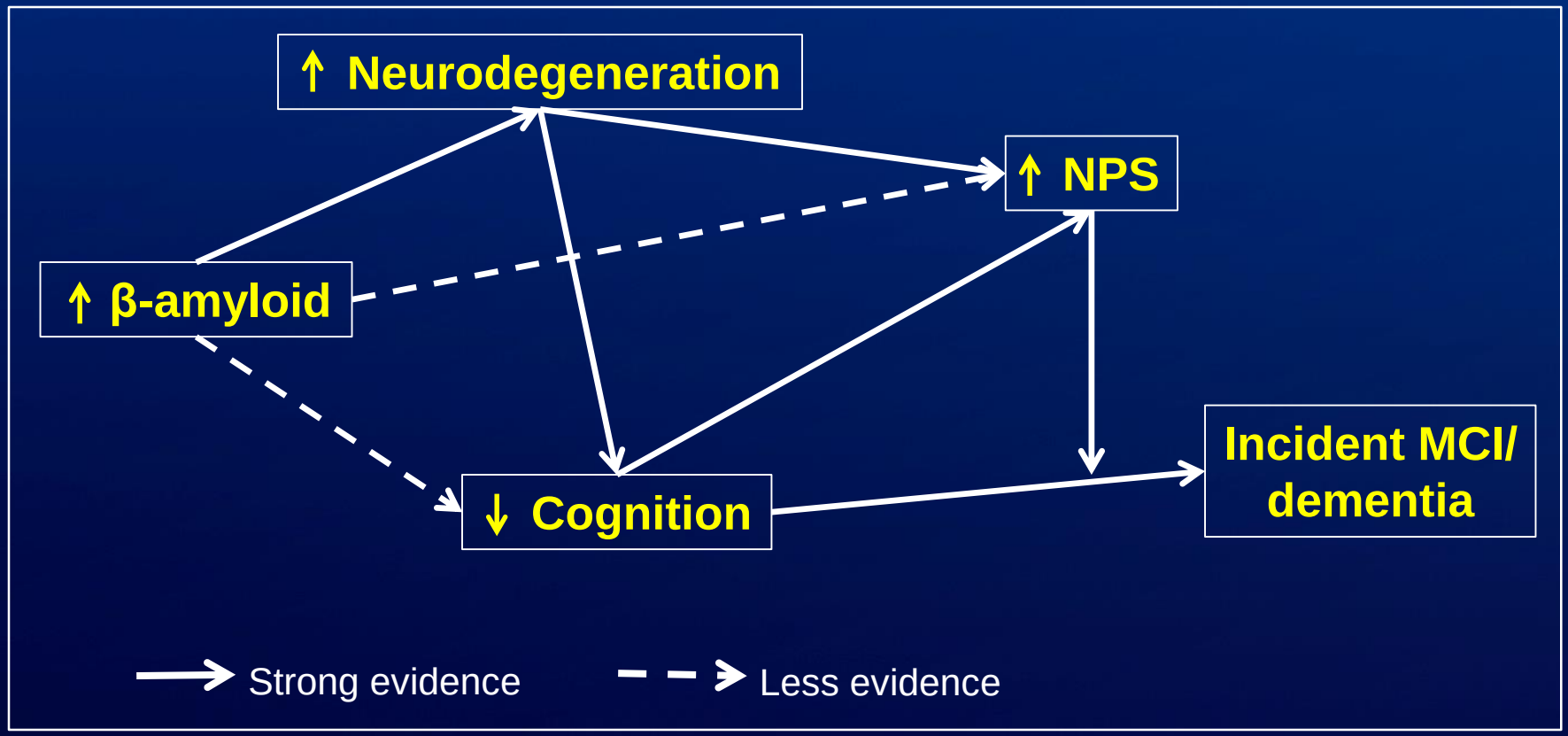
Theoretical model linking NPS with AD biomarkers and cognitive outcomes



Geda et al. 2017. American Journal of Geriatric Psychiatry

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