Vascular Disease in the Brain: An Important Cause of Dementia?

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Vascular Disease and Dementia

1. Vascular Disease in the brain is an independent determinant of dementia with or without clinical stroke

2. Subcortical infarcts and high white matter grade are risk factors for dementia? How?

3. Vascular "dementia" is primarily a frontal lobe disease as compared to Alzheimer's Disease (Jagust)

4. Small vessel cortical micro infarcts are a "cause" of dementia and are correlated with measurable vascular disease (White)

5. Decreased cortical perfusion (hypo perfusion) is a cause of Alzheimer's Disease (De La Torre)

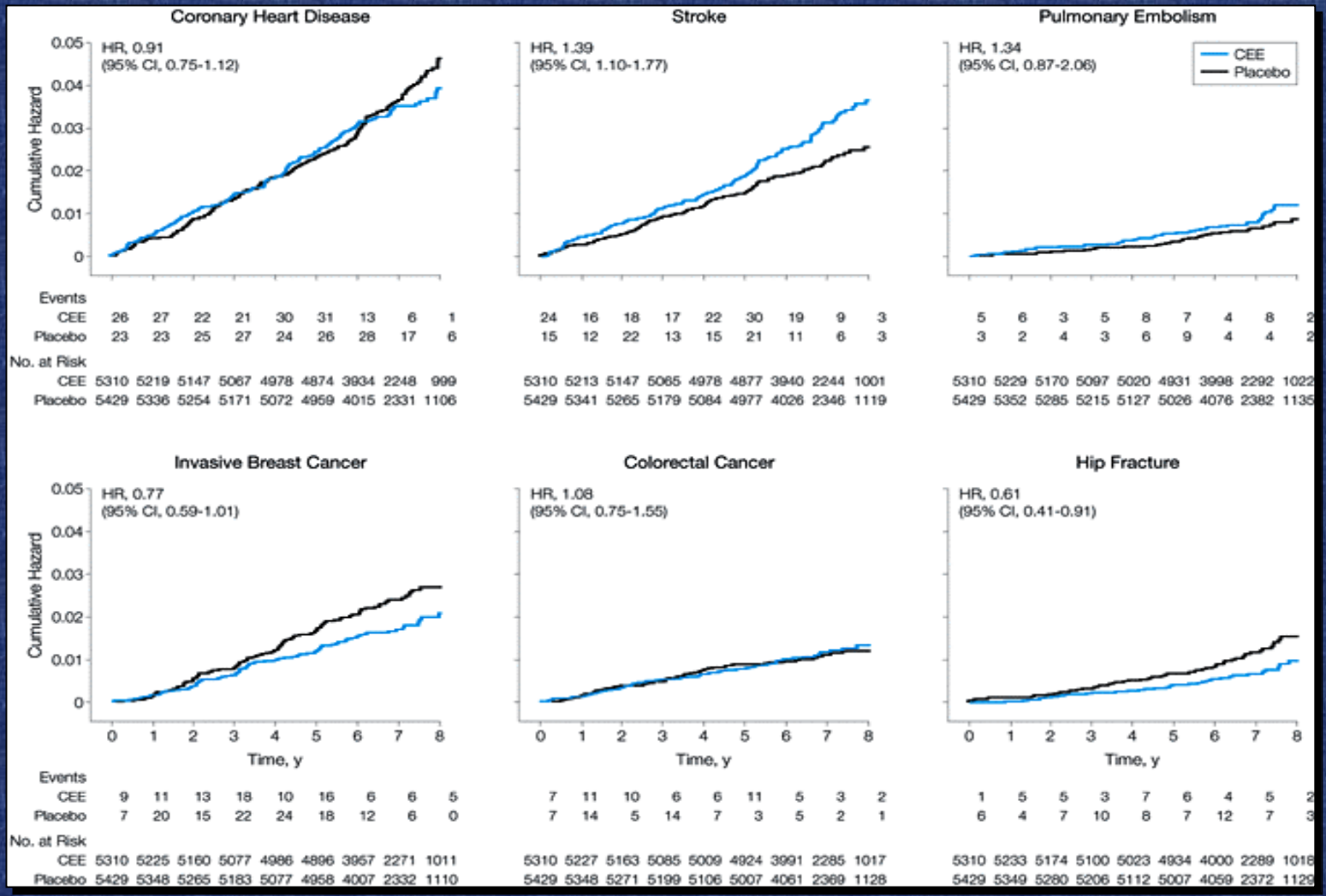
Vascular Disease and Dementia (cont'd)

6. Cholesterol metabolism in the brain is related to production of beta amyloid and amyloid plaques; animal models consisted with a primary role of dietary cholesterol and fat (Sparks)

7. Vascular injury leads to inflammation and deposition of beta amyloid, especially amyloid angiopathy (Burgermeister)

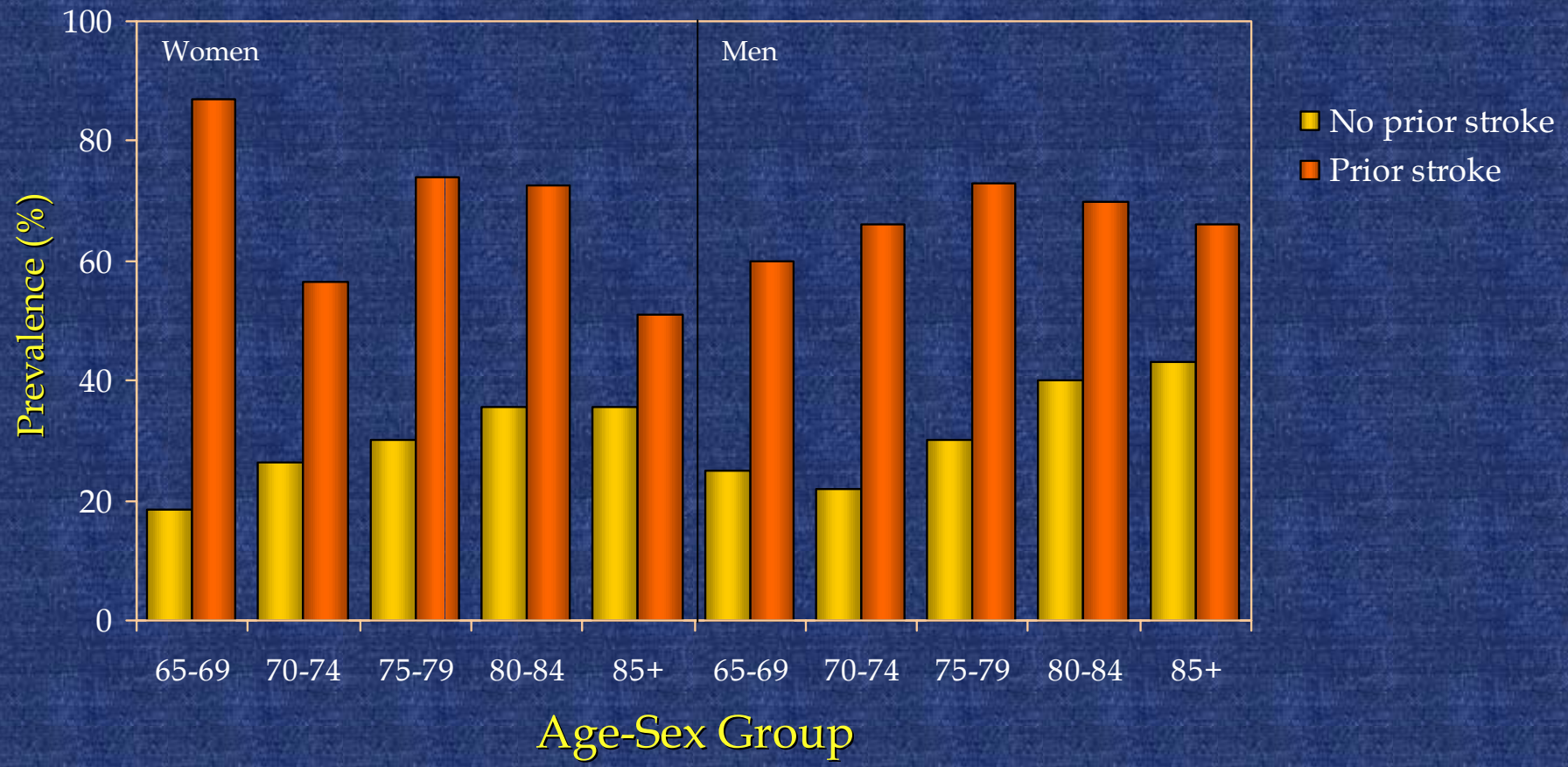
8. Vascular disease is common to the elderly, as is dementia, but not causal in most cases

Kaplan-Meier Estimates of Cumulative Hazards for Selected Clinical Outcomes



The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. The Women's Health Initiative Randomized Controlled Trial. JAMA 2004;291(14):1701-1712

Prevalence of MRI Infarct by Sex, Age and Prior Stroke



Kuller LH, Fried LP, Kronmal RA. The importance of preclinical disease: lessons from the Cardiovascular Health Study. In: Wenger NK (Editor). Cardiovascular Disease in the Octogenarian and Beyond. Martin Dunitz Ltd 1999, pp 43-58

Comparison of Clinical Criteria for Vascular Dementia

	DSM-IV	ICD-10	ADDTC Probable IVD	NINDS-AIREN Probable VaD
Ischemic stroke	+	+	+	+
Hemorrhage	+	+	-	+
Stepwise deterioration	-	-	-	+ (1)
'Patchy' distribution of cognitive deficits	-	+	-	-
Focal neurological signs	+	+	-	+
Focal neurological symptoms	+	-	-	-
Evidence of significant CVD	+	+	+ (2)	+
Etiological relation to the disturbance	+	+	-	+
Temporal relationship between stroke and dementia	-	-	+ (2) In cases where there is a single stroke	+ (1)
Structural neuroimaging	-	-	One infarce outside cerebellum	Multiple large vessel strokes or multiple lacunes or extensive WMLs or single strategically placed lesion

Erkinjuntti T, Roman G, Chui H. Diagnostic criteria. In: Erkinjuntti T, Gauthier S (eds). Vascular Cognitive Impairment. Martin Dunitz, Ltd, London, England. 2002 Ch 4 pp 43-57

CHS Cognition Study: MRI Follow-up

CHS
5888 participants 65+
(4 Centers)
Medicare sample
1989-90, 1992-93

→

MRI Brain
1992-94
3608

→

Measurement of incidence of dementia

2nd MRI: 2112
1997-99

↓

1581 Normal
301 MCI
195 Incident dementia between MRI's
35 Prevalent dementia at first MRI

The presence or absence of dementia and, possibly, type of dementia was first determined. The preMRI classification of the type of dementia was based on the evaluation of the clinical information including all of the neuropsychological and neuropsychiatric evaluation over time and history of clinical stroke but did not include the MRI evaluation. Information from the MRI was then used to classify the specific type of dementia.

Kuller LH, Lopez OL, Jagust WJ, Becker JT, DeKosky ST, Lyketsos C, Kawas C, Breitner JCS, Fitzpatrick A, Dulbert C. Incidence and determinants of vascular dementia with and without Alzheimer's disease in the Cardiovascular Health Cognition Study. (in preparation)

We have classified VascD primarily by a modified ADDTC criteria (ADDTC VascD). For VascD, we have used the history, examination by neuroimaging of a single stroke with or without clearly defined temporal relationship to the onset of dementia or evidence of Binswanger syndrome including subclinical brain infarcts and extensive white matter changes on neuroimaging.

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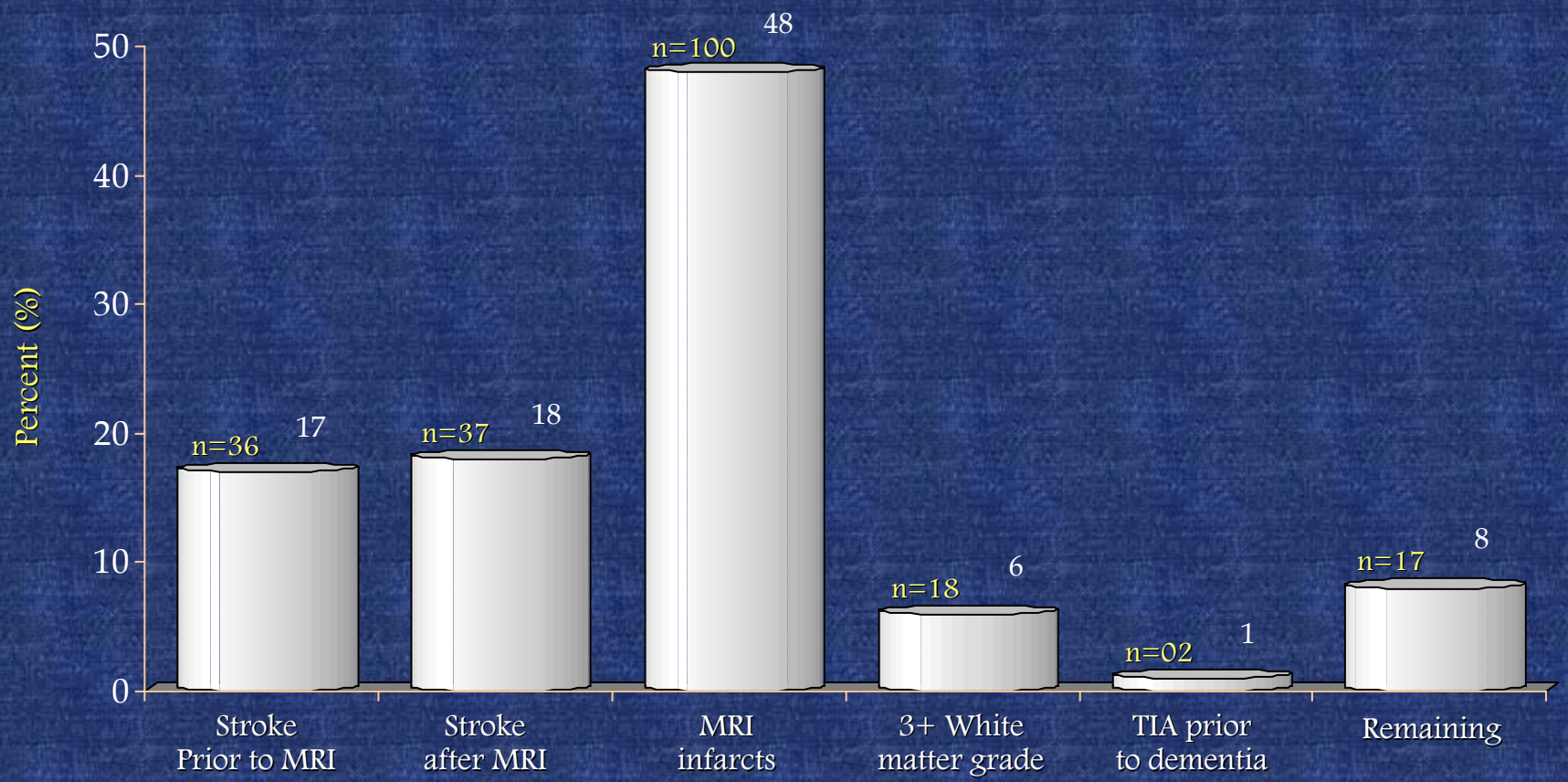
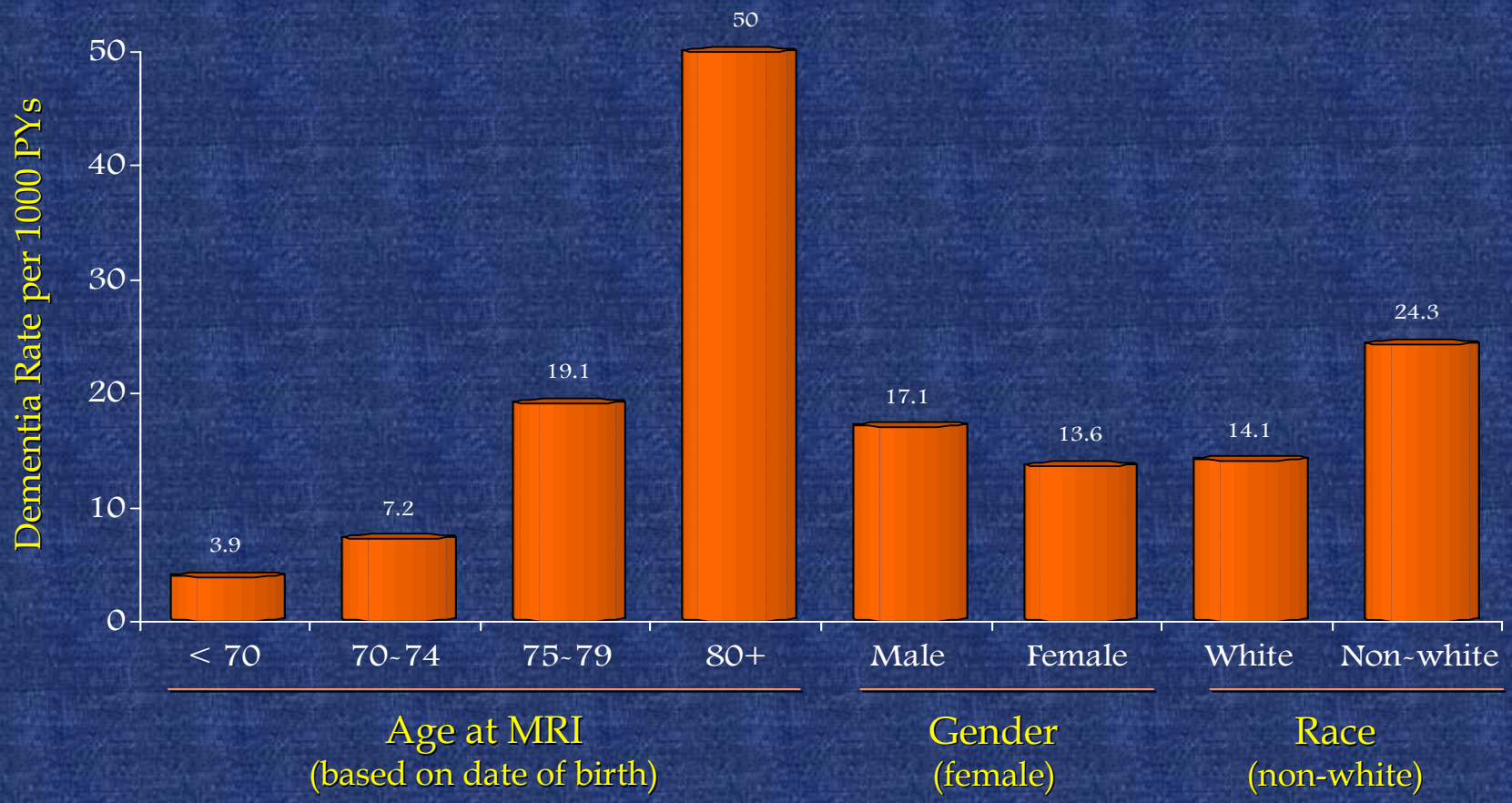
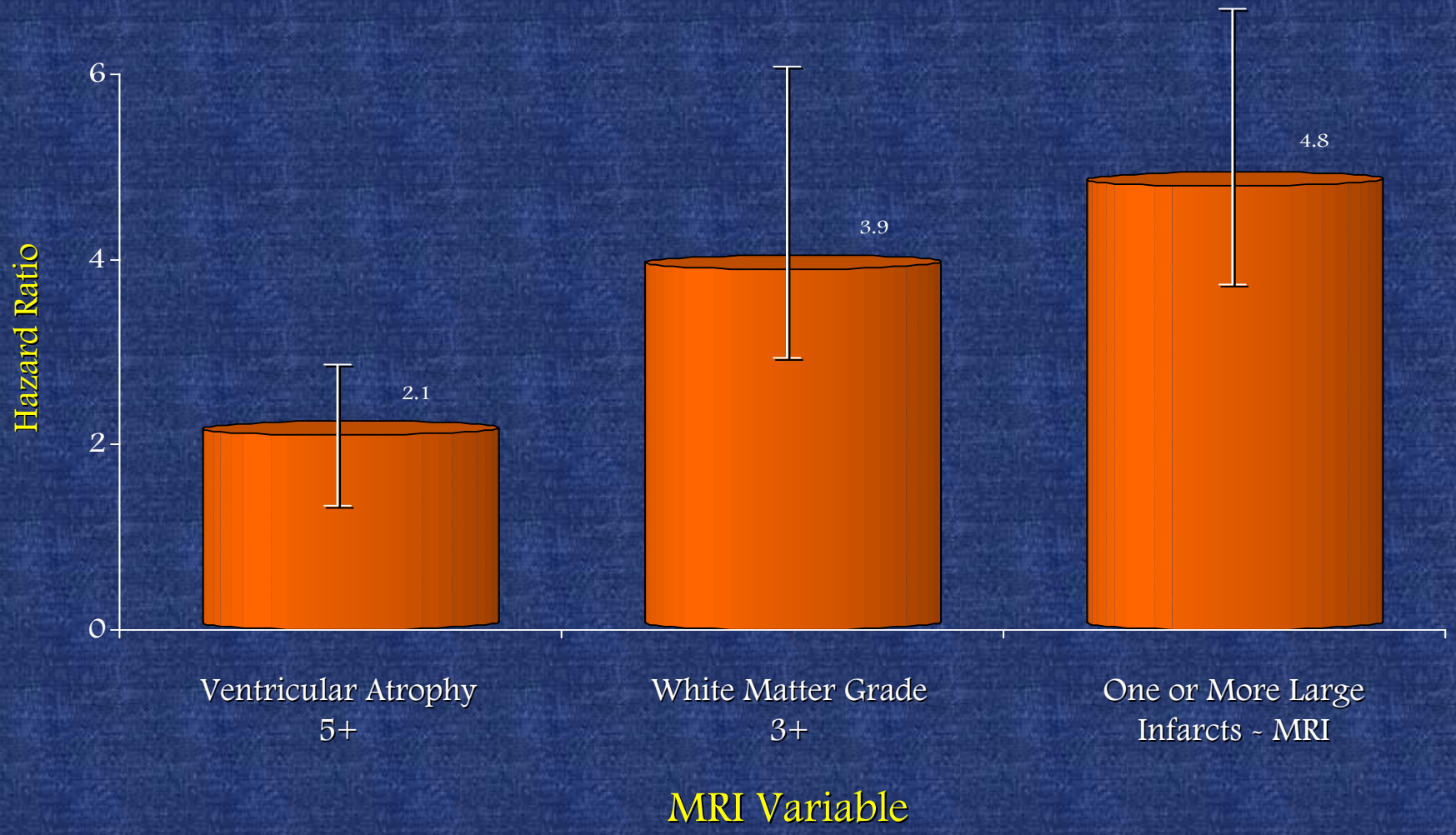
Criteria for Vascular Dementia by ADDTC Criteria



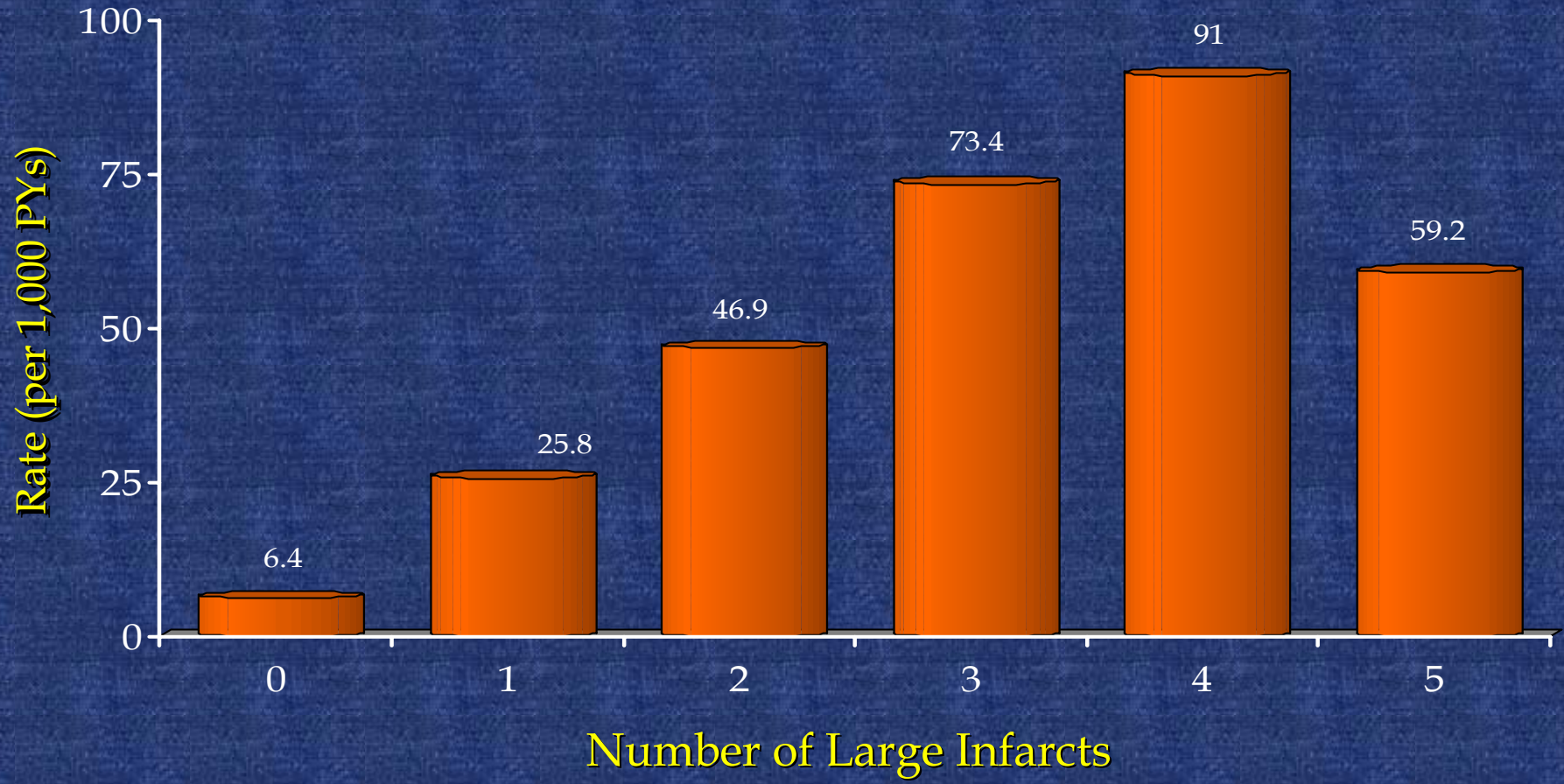
Incidence of Vascular Dementia (by ADDTC Criteria) by Age, Sex and Race



MRI Variable 1992-94, Risk of Incident Vascular Dementia by ADDTC Criteria, Age Adjusted



Percent of VaD Within Subgroups and Incidence of VaD by Baseline MRI Findings



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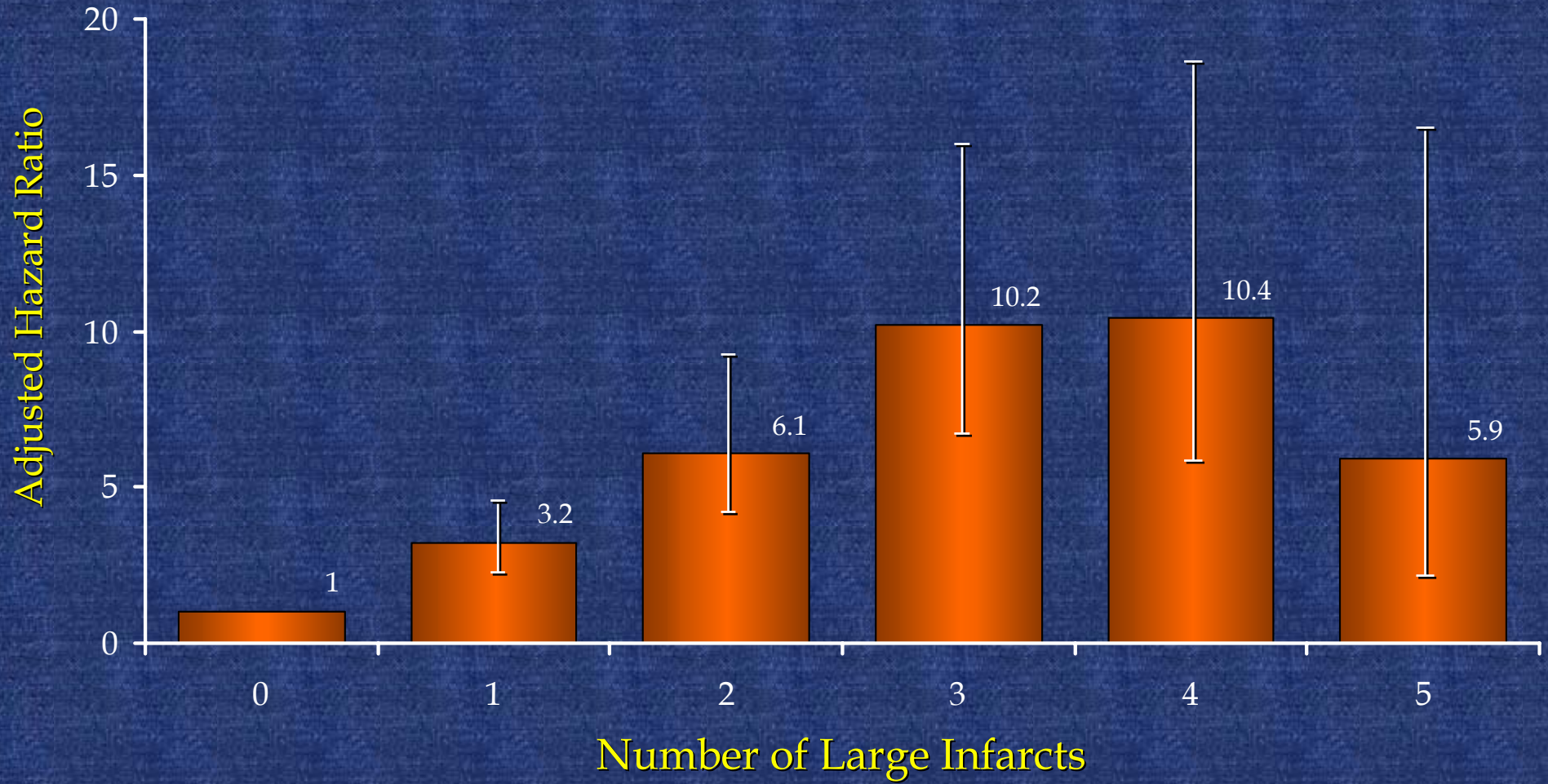
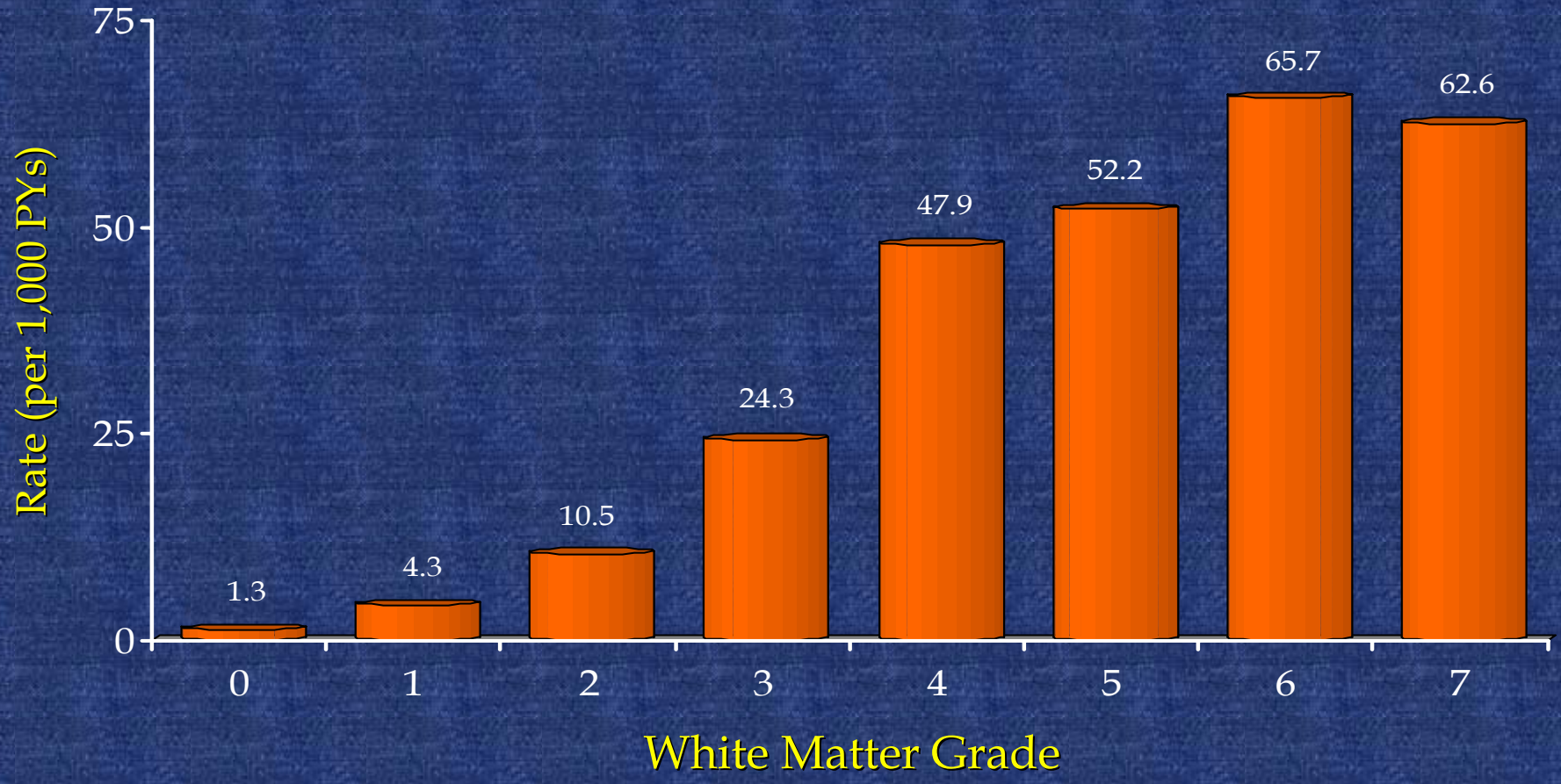


Location of Brain Infarcts ≥ 3mm: ADDTC vs. Normal; No Prior History of Stroke (first infarct only)

	Normal		Vascular Dementia	
	N	%	N	%
Cortical	49	09	13	11
Cerebellar	22	04	07	06
Deep Cerebellar	14	03	06	05
Basal Ganglia	395	73	84	71
Brain Stem	07	01	~	~~
Deep White Matter	52	10	08	07
TOTAL	539	100	118	100

Percent of VaD Within Subgroups and Incidence of VaD by Baseline MRI Findings



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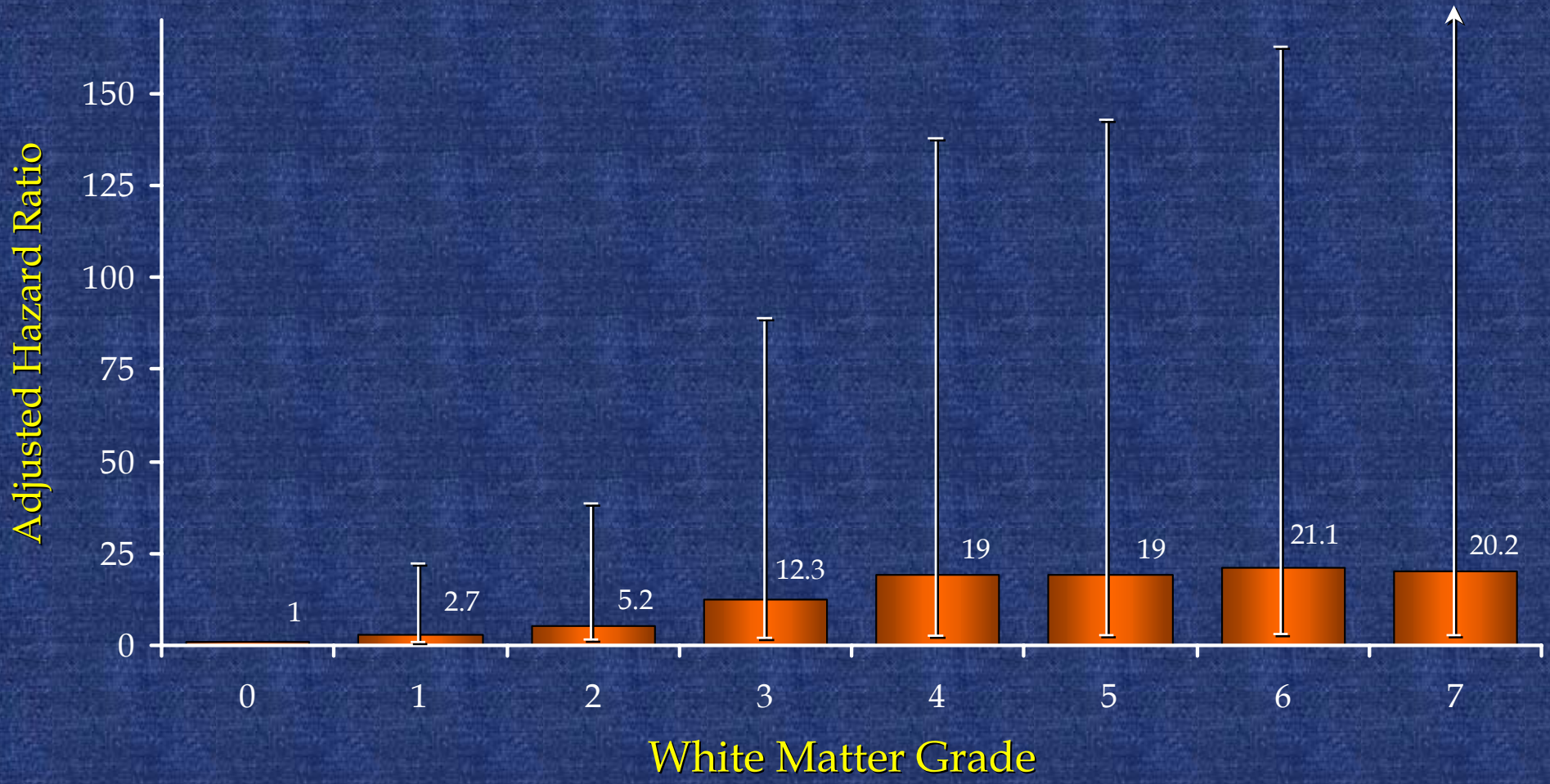
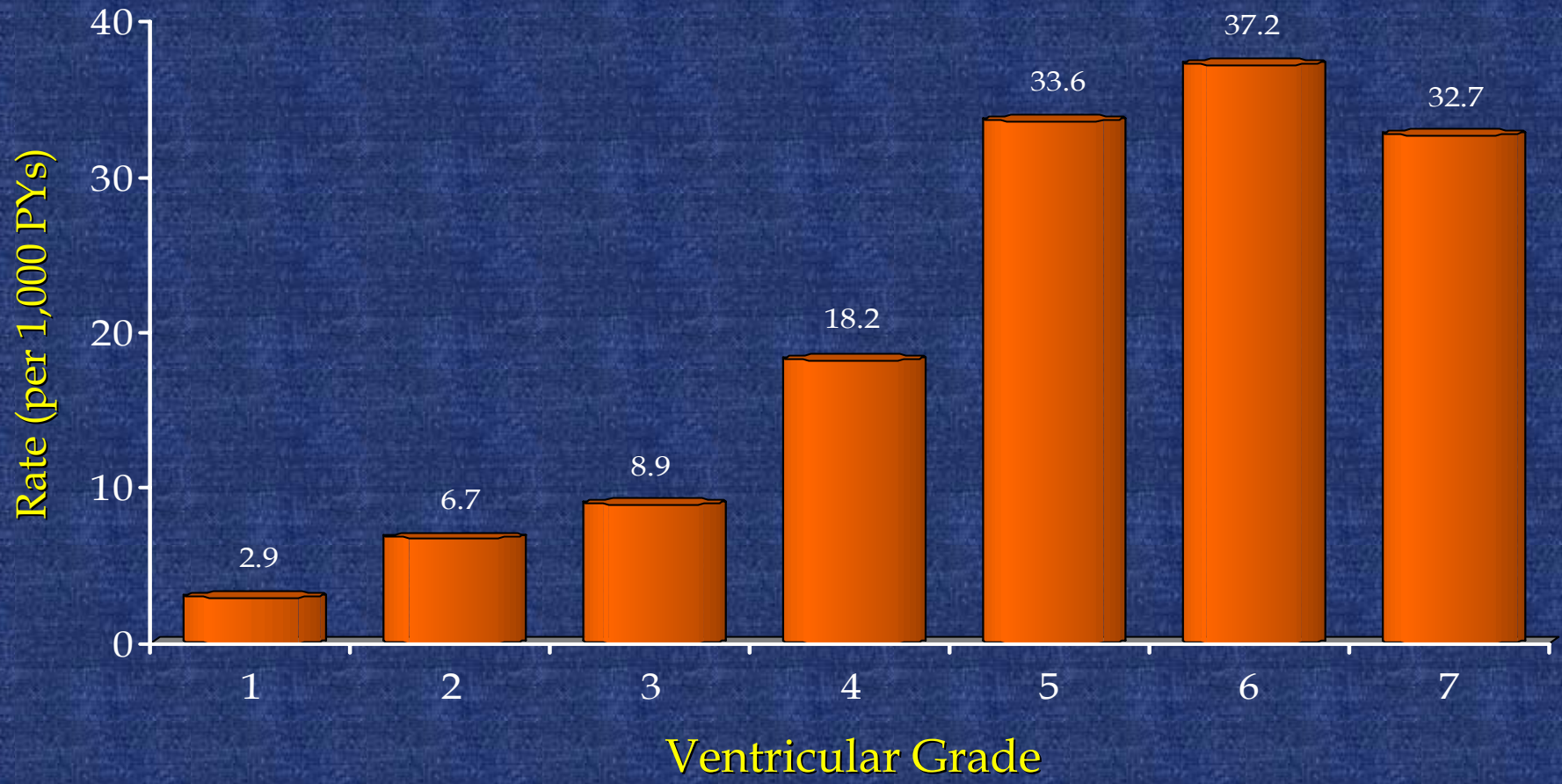
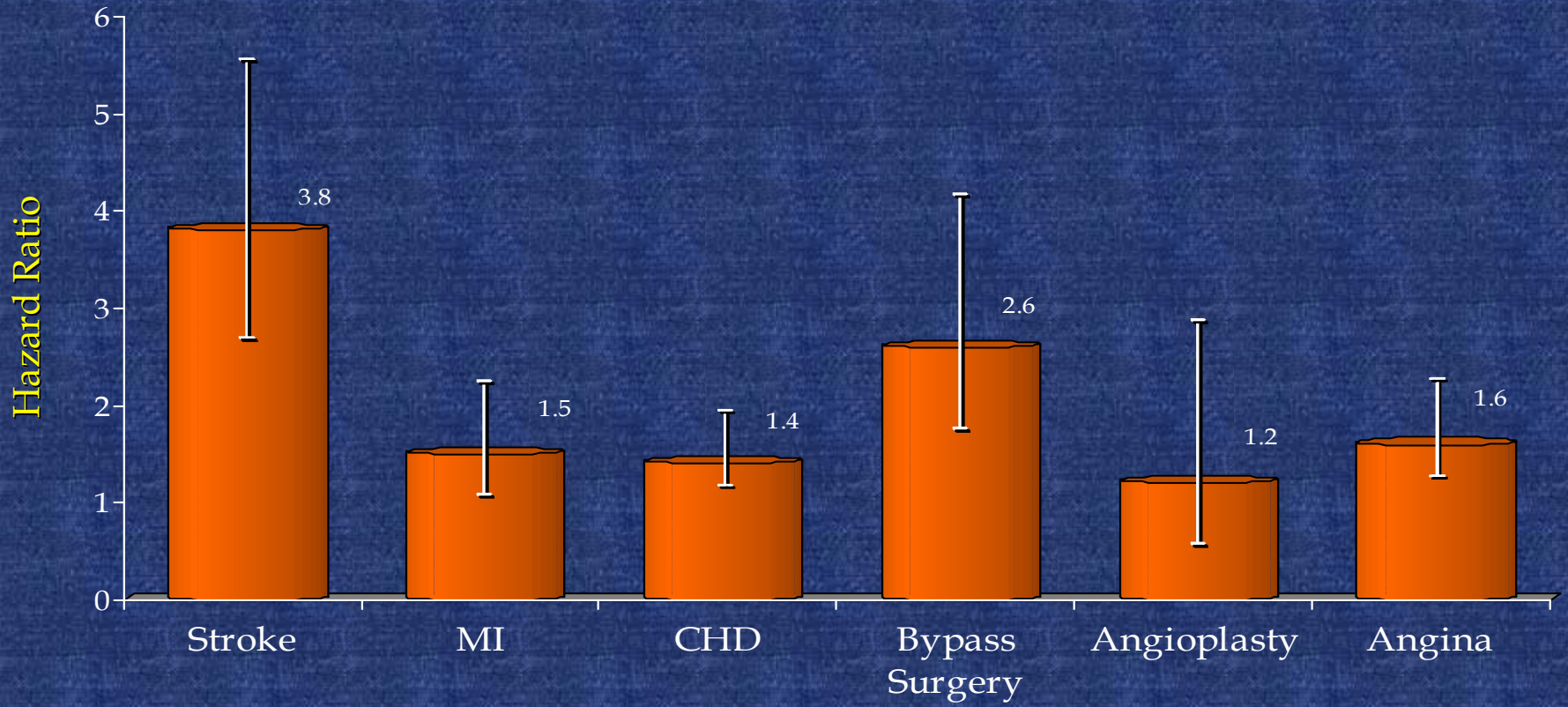


Percent of VaD Within Subgroups and Incidence of VaD by Baseline MRI Findings



Hazard Ratios for ADDTC VascD by Cardiovascular and Cerebrovascular Disease Diagnosis at Baseline (adjusted for age, race, sex): n=213 VascD cases; 2318 normal



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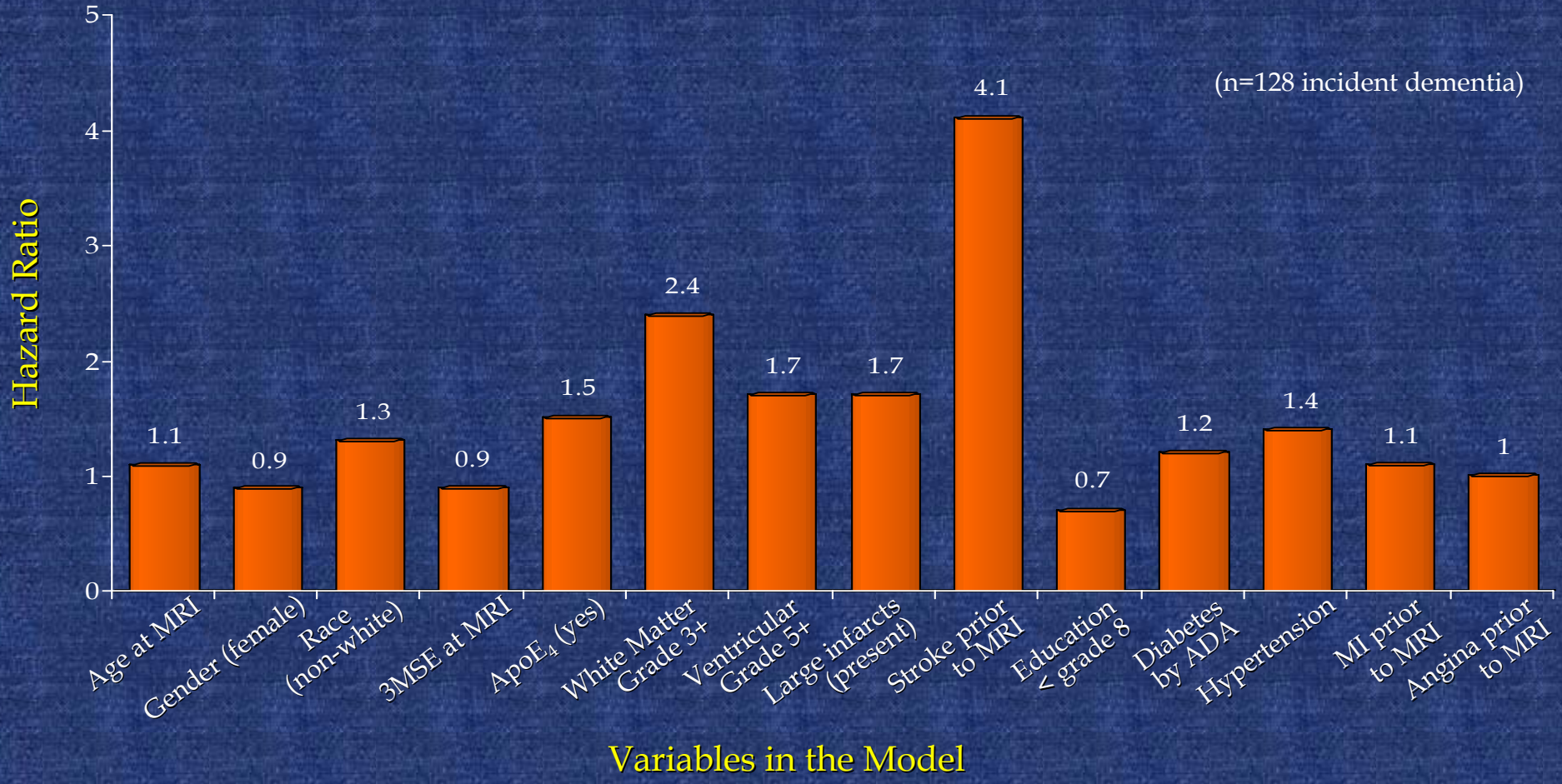
Distribution of ADDTC Vascular Dementia and ADRDA – Alzheimer's Disease

ADDTC VascD Possible/Probable		Incident Cases of Dementia *NOT* ADDTC VAD	
NINCDS-ADRDA Criteria for AD		NINCDS-ADRDA Criteria For AD	
Not Present (n=61) (13.3%)	Probable/Possible (n=151) (33.1%)	Probable/Possible (n=245) (53.6%)	Total n=457 (100%)

Results of Cox Survival Analysis of Risk of Vascular Dementia According to pre-MRI Review vs. Normals



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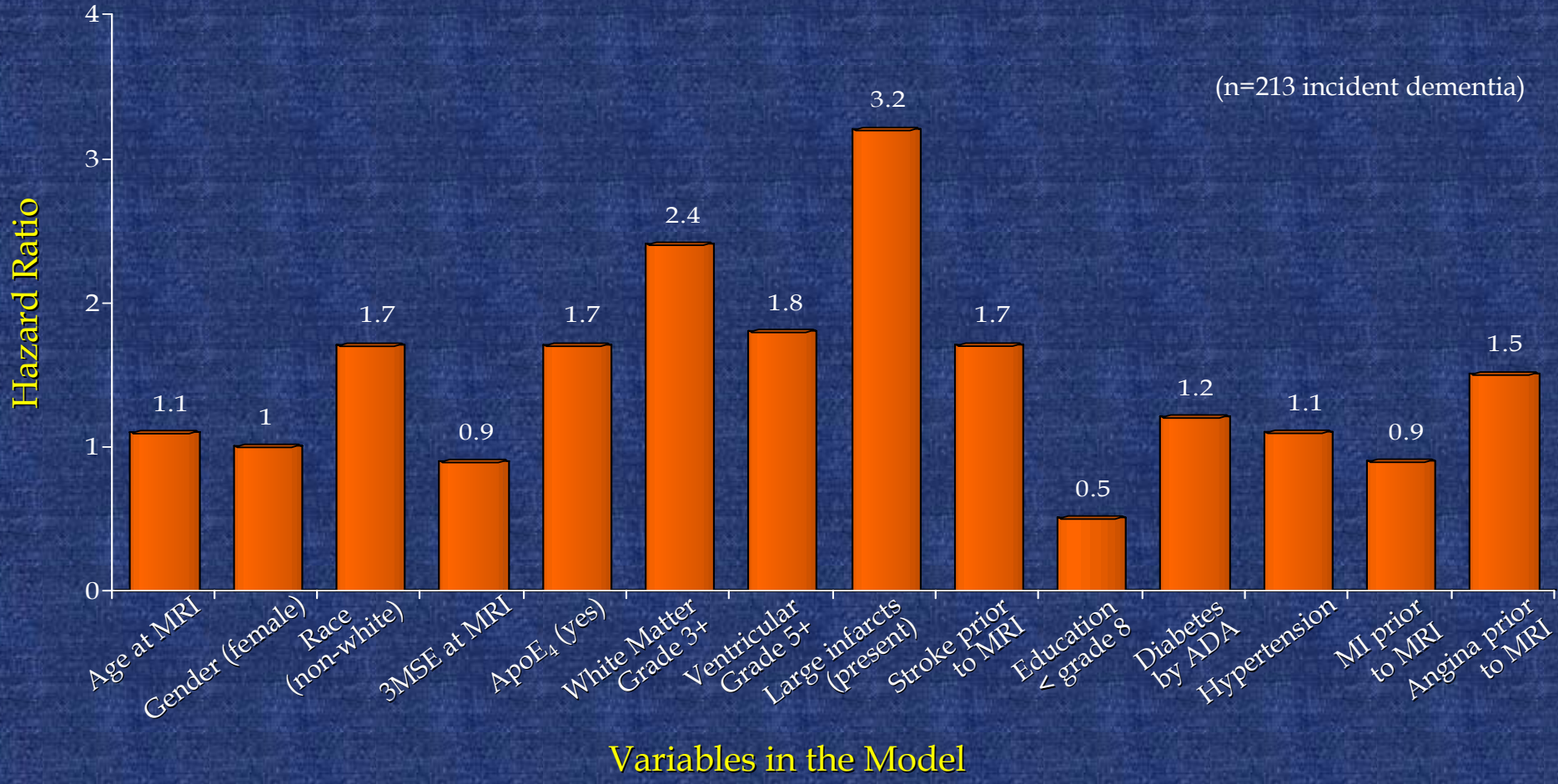

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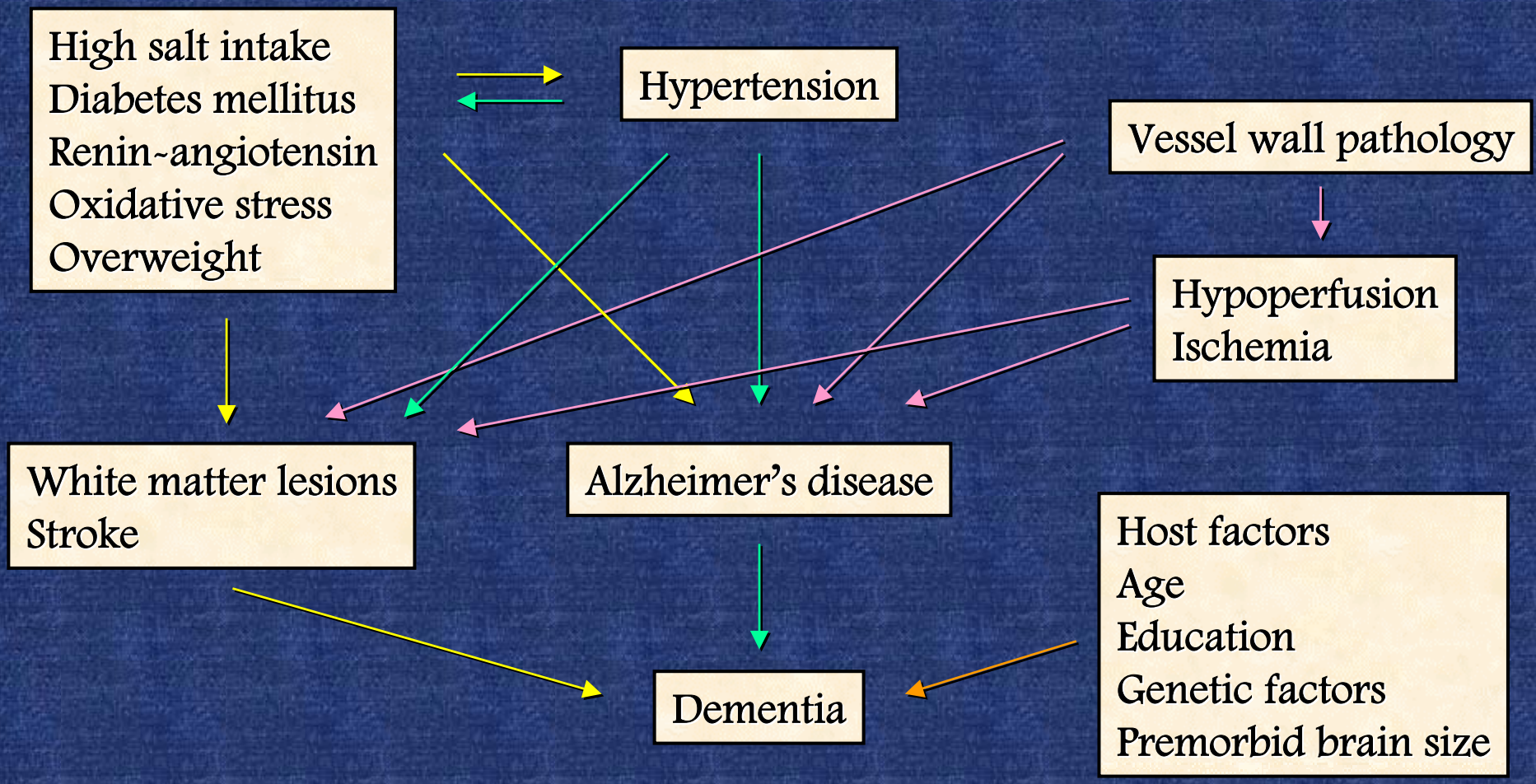
Possible Mechanisms



Skoog I, Gustafson D. Hypertension and related factors in the etiology of Alzheimer's Disease. Ann NY Acad Sci 2002;977:29-36

Conclusions

I. Prevalence of vascular disease in brain based on MRI is very high

II. Incidence of vascular dementia based on MRI and clinical criteria is higher than reported

III. Without MRI cannot discriminate vascular and Alzheimer's Disease (AD) in many cases (mixed dementia)

IV. Vascular disease may contribute to pathogenesis of Alzheimer's Disease or be independent component, i.e., two diseases

V. Need to test whether treatment of risk factors will:
   a. Reduce prevalence of vascular brain disease
   b. Reduce incidence of clinical dementia

VI. Prevention of vascular brain pathology by aggressive risk factor modifiers could have a major impact on incidence and disability to dementia

Classification Revised of Type of Dementia

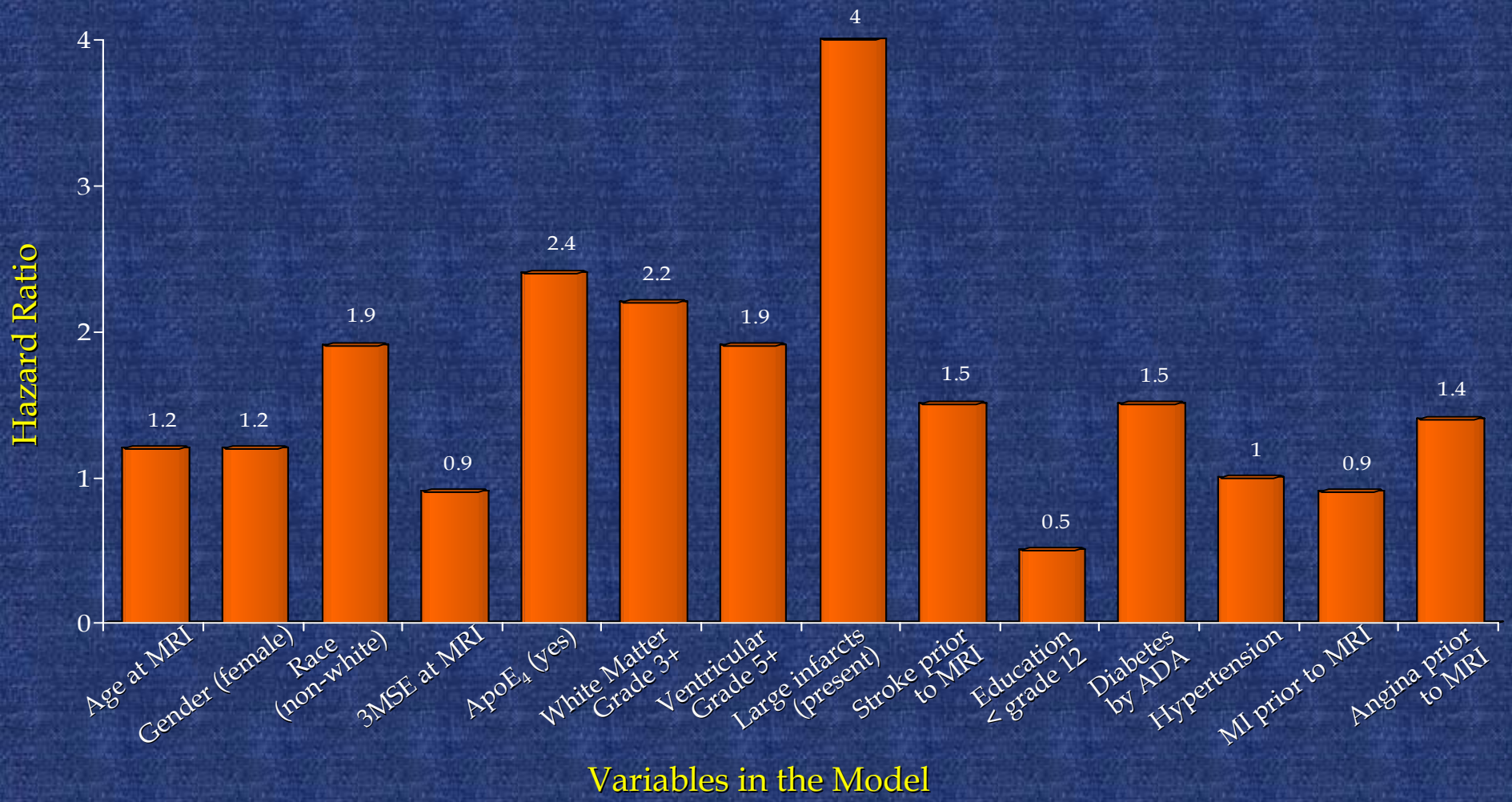
1. Dementia: yes – no

2. History of stroke and characteristics: yes - no

3. MRI:
   a. Extent of white matter grade
   b. Cortical and subcortical infarcts
   c. Global ventricular atrophy
   d. Focal atrophy: hippocampus, etc.

4. Neurological and cognitive test-specific abnormalities

Cox Model Comparing ADDTC VascD Possible/Probable -- NINCDS-ADRDA Criteria for AD Probable/Possible vs. Normals



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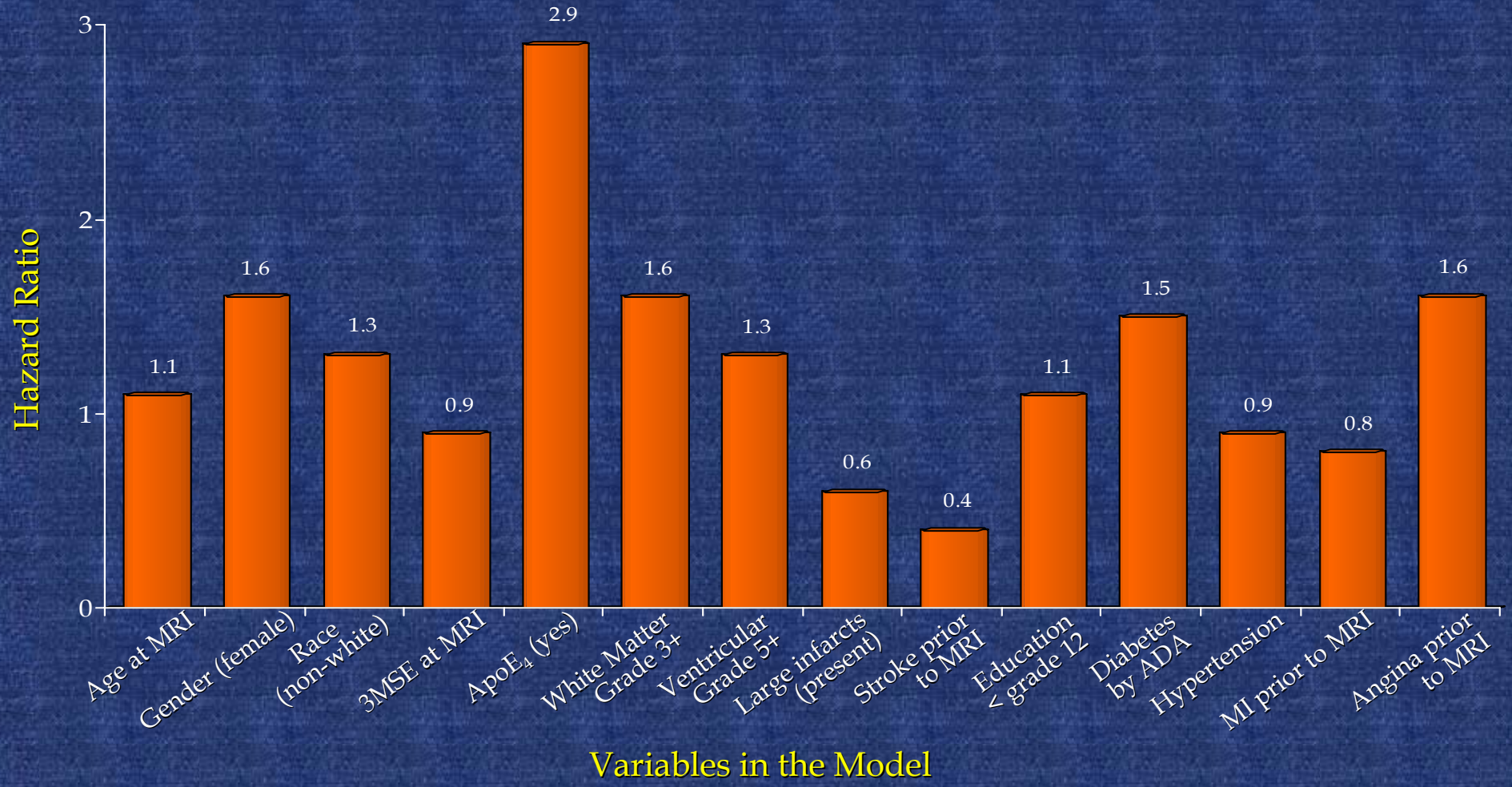
Cox Model Comparing NOT ADDTC VascD Possible/Probable -- NINCDS-ADRDA Criteria for AD Probable/Possible vs. Normals



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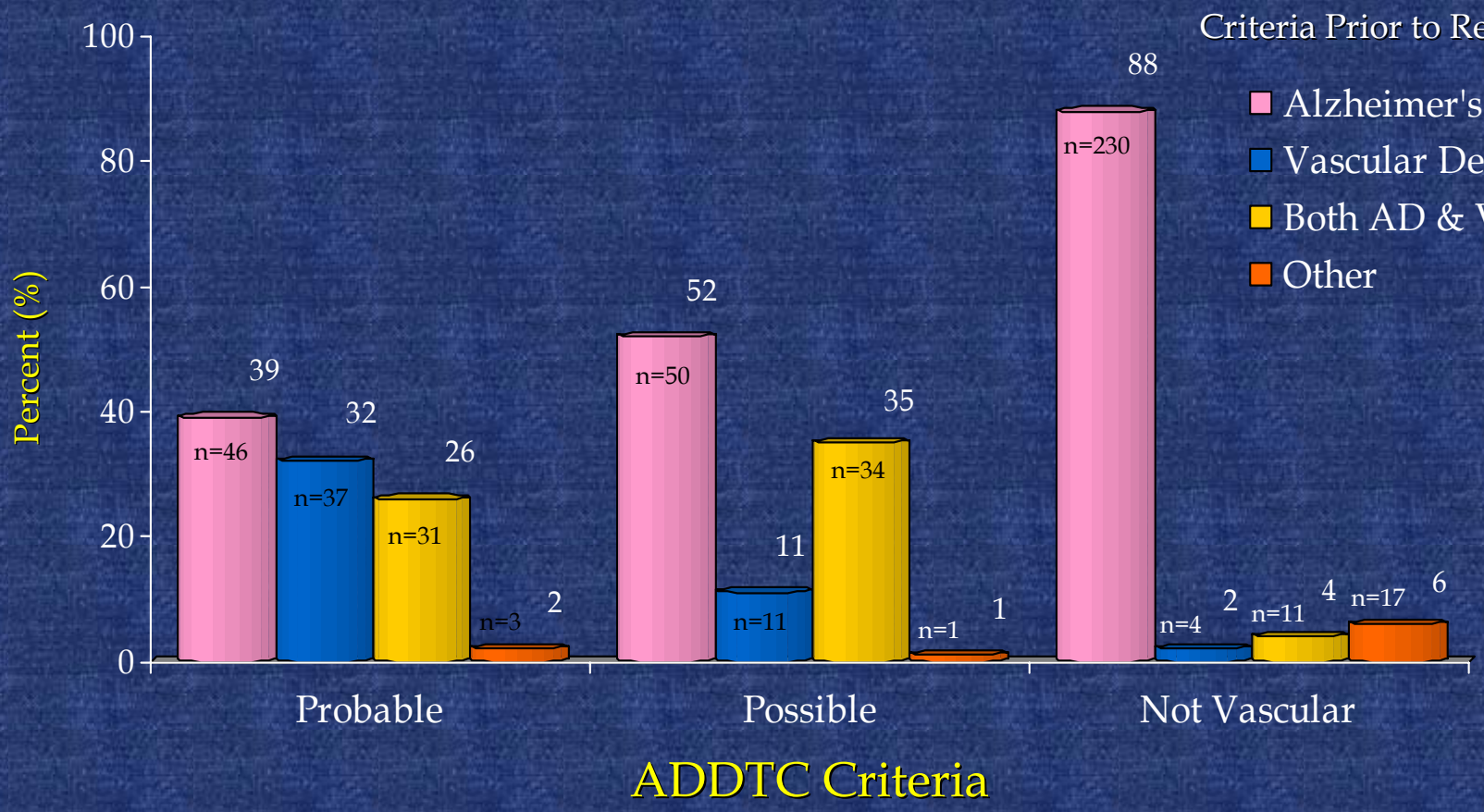
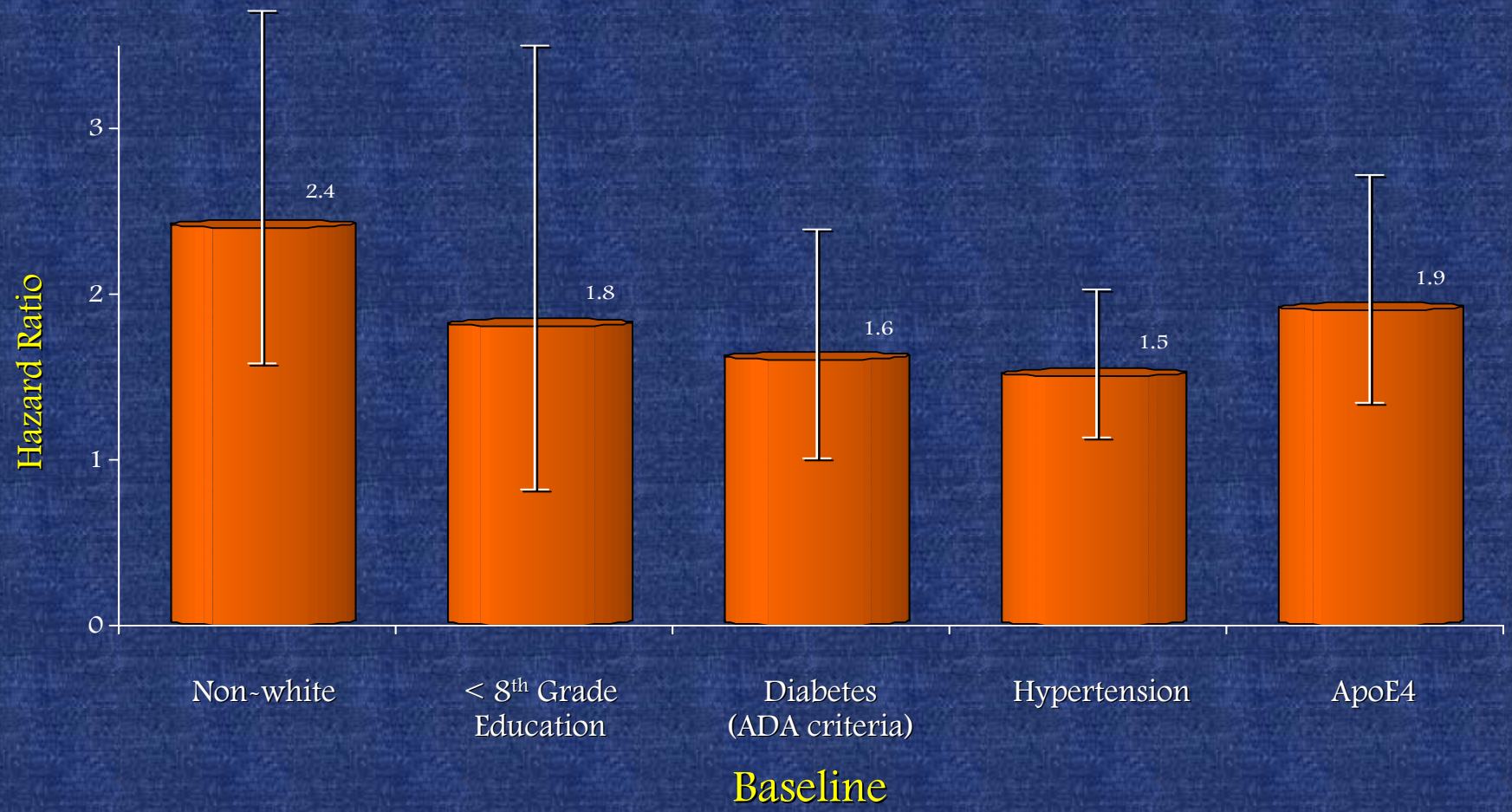
MRI Methods

Participants without contraindication, who consented, underwent MRI in a standard fashion including standard sagittal and axial spin echo T1-weighted images (TR/TE 500/ 15-25) and axial spin density and T2-weighted images (TR/TE 3000/20-35/70-100), all with 5mm thickness and no interspace gaps *(Manolio TA, Stroke 1994), (Bryan RN, Neurorad 1994)*.

Distribution of Vascular Dementia Based on Different Criteria Using MRI and Clinical Data (480 Incident Dementia, CHS)



Hazard Ratios for Vascular Dementia Probable and Possible by ADDTC -- Incident Cases (age-adjusted)



Distribution of Cases Included and Not Included in the CHS Cognitive Study by Reason of Exclusion

1	Total CHS participants	5,888
2	Participants who did not have the MRI due to	
	Death before the MRI	411 (7.0)
	Illness	743 (12.6)
	Refused the MRI	575 (10)
	Missed clinical visits	431 (7.3)
	Other causes	68 (1.2)
3	Participants who had an MRI in 1992-1993	3,660 (62)
4	Total participants entered in the CHCS	3,608 (61.2)

Lopez OL, Kuller LH, Fitzpatrick A, Ives D, Becker JT, Beauchamp N. Evaluation of dementia in the cardiovascular health cognition study. Neuroepidemiology 2003;22:1-12

The classification of specific types of dementia by different categories of classification after the review of the MRI were based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV), National Institute of Neurological Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINDS-ADRDA), State of California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC), National Institute of Neurological Diseases and Stroke - Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria.

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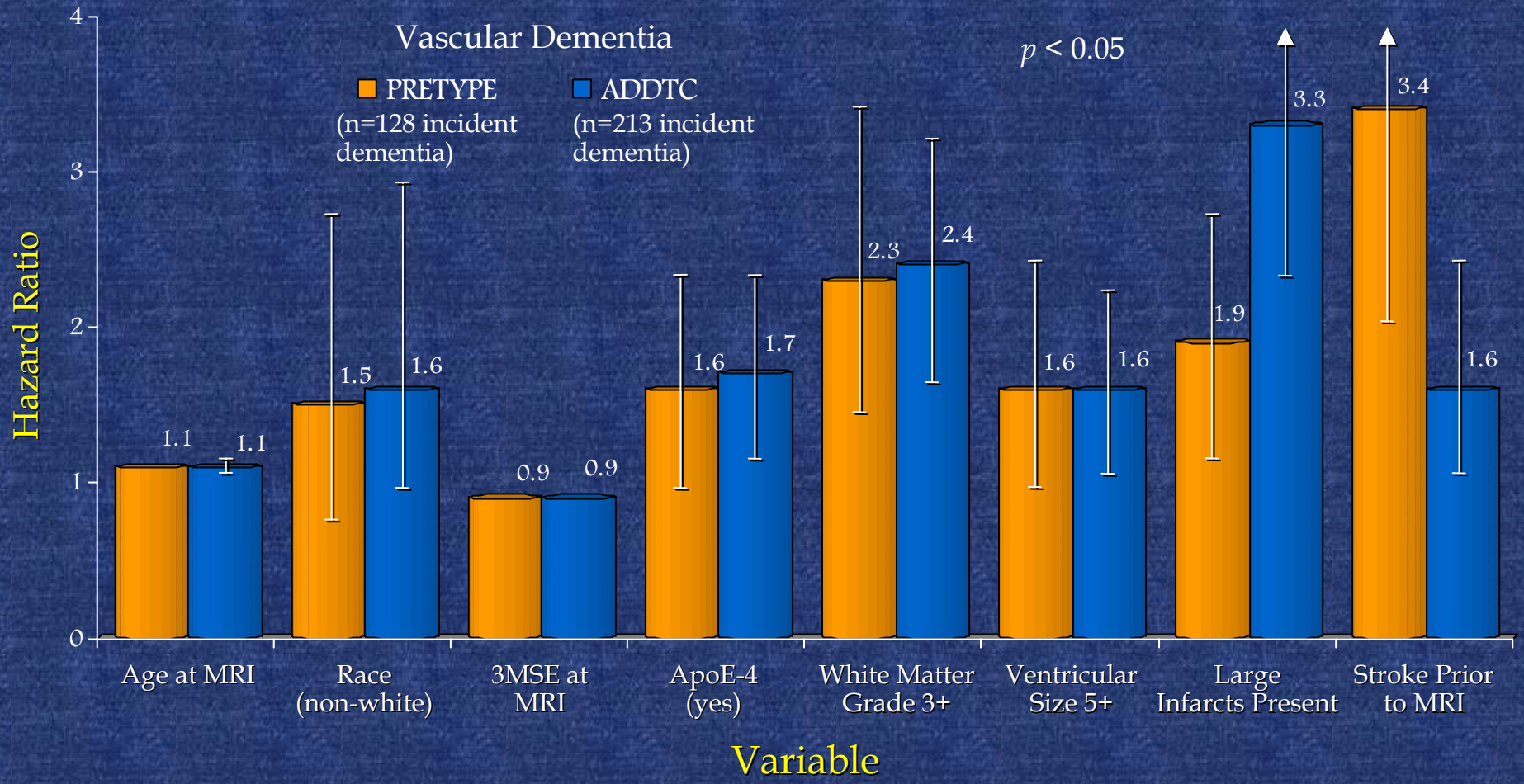
Results of Cox Survival Analyses of Risk of Vascular Dementia According to PRETYPE and ADDTC CRITERIA versus Normals (excluding MCI)



Age-Adjusted Scores on Tests of Cognitive Function and Depression, by Treatment Group

Test (Score Range*)	Estrogen/Progestin (n=517)	Placebo (n=546)	Difference† (95% Confidence Interval)	*P* Value
	Mean ± SD			
Modified Mini-Mental Status (0-100)	93.1 ± 6.4	93.4 ± 6.4	-0.4 (-1.1 to 0.4)	0.36
Verbal Fluency (0 - ∞)	15.9 ± 4.8	16.6 ± 4.8	-0.7 (-1.3 to -0.1)	0.02
Boston Naming (0 – 30)	14.0 ± 1.4	14.1 ± 1.4	-0.1 (-0.3 TO 0.1)	0.34
Word List Memory (0 – 30)	19.7 ± 3.9	20.1 ± 3.9	-0.5 (-1.0 TO 0.02)	0.06
Word List Recall (0 – 10)	6.4 ± 2.1	6.6 ± 2.1	-0.1 (-0.7 TO 0.4)	0.29
Trails B (0 – 300)	156.2 ± 77.5	151.5 ± 77.5	4.6 (-4.9 TO 14.2)	0.34
Geriatric Depression Scale (0 – 15)	2.0 ± 2.6	2.0 ± 2.6	0.001 (-0.3 TO 0.3)	0.99

•Higher scores reflect better cognitive function on all tests except Trails B, where a lower score reflects better cognitive function. Higher scores on the Geriatric Depression Scale reflect more depressive symptoms.

† Estrogen/progestin group minus placebo group. A negative difference indicates a worse score in the estrogen/progestin group for all tests except Trails B and Geriatric Depression Scale.

Grady D, Yaffe K, Kristof M, Lin F, Richards C, Barrett-Conor E. Effect of postmenopausal hormone therapy on cognitive function: the Heart and Estrogen/progestin Replacement Study. Am J Med 2002;113:543-548