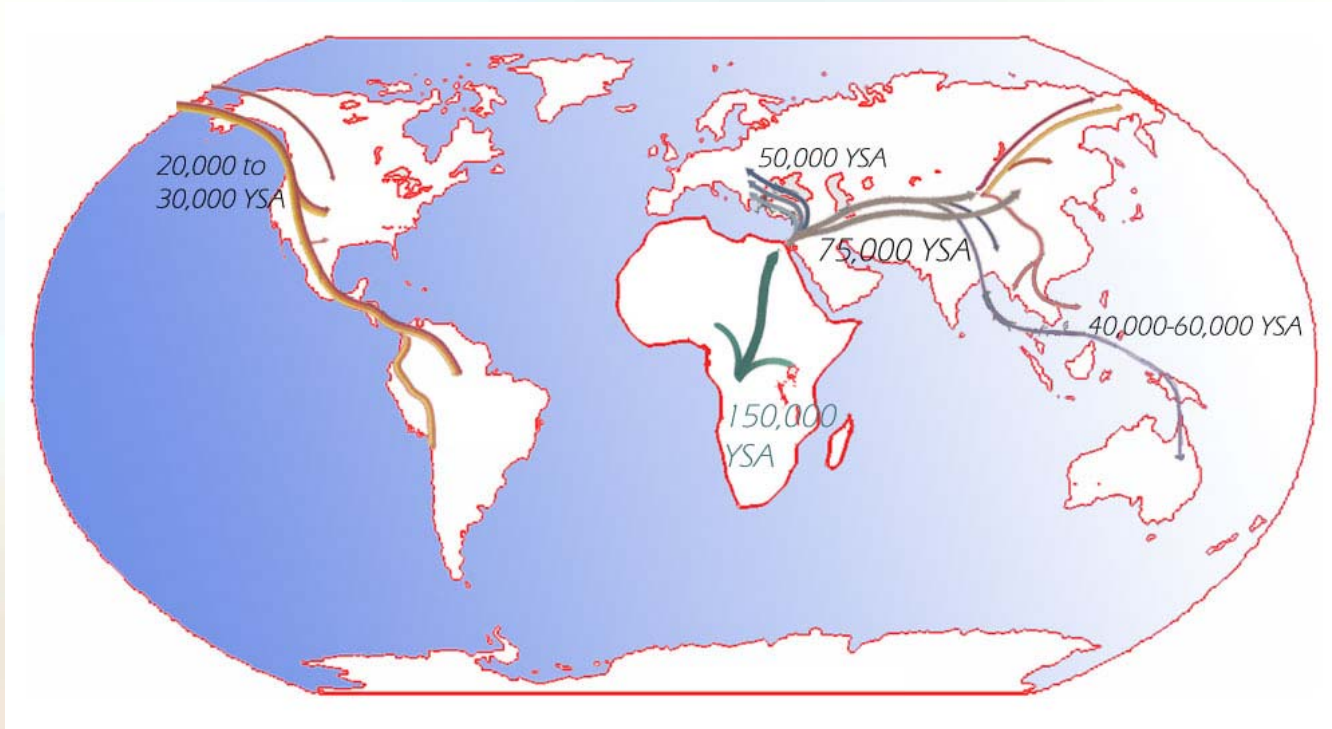


Why study dementia in diverse populations? Results from the Sacramento Area Latino Study on Aging



MN Haan, Professor, Epidemiology
University of Michigan



**Funding: NIA AG 12975, DK 60753, AG10129, AG10220; USDA 00-35200-9073
Robert Wood Johnson Scholars (045823), Claude Pepper Center (F014308)**

Acknowledgements

University of Michigan,

- Allison E Aiello
- Sharon Kardia
- Rod Little
- Lewis Morgenstern
- Caroline Blaum
- Laila Poisson
- SALSA staff

University of California, Davis

- Dan Mungas
- Ladson Hinton
- SALSA staff
- Josh W Miller
- Ralph Green
- Marisa Ramos
- Lindsay Allen
- Charles DeCarli

University of California, Berkeley

- William Jagust

University of California, San Francisco

- Kristine Yaffe
- Kala Mehta

Kaiser Permanente Division of Research

- Rachel A Whitmer

University of Washington

- Paul Crane
- Suzanne Craft

Wayne State University, IOG

- Hector Gonzalez

What is meant by diversity?

Elements of understanding ethnic and ancestral differences

International or Regional differences

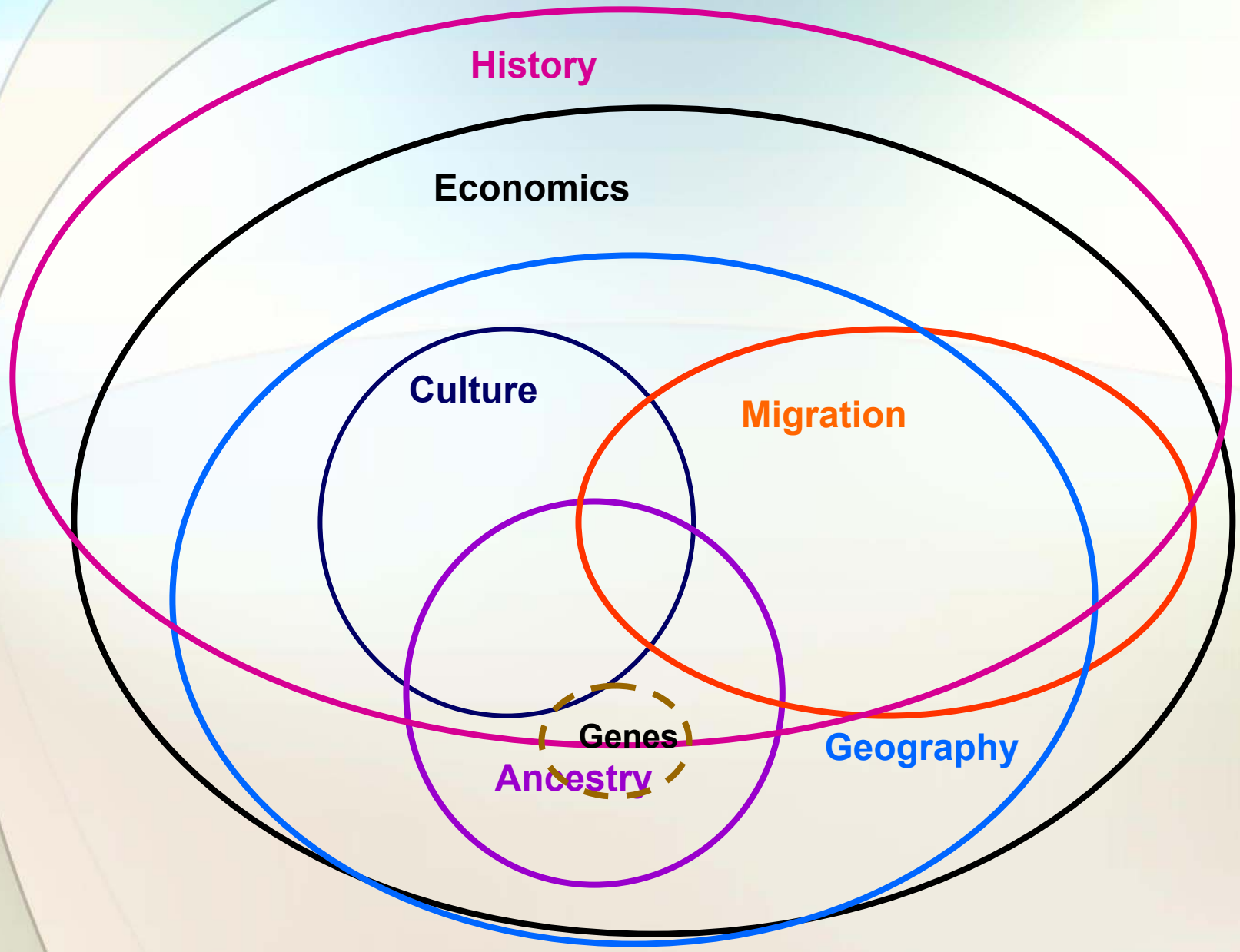
- Culture, economics and ancestry in different locations

Cross-cultural differences

- Culture, economics and ancestry of different groups living within the same/proximal geography

Changing places or changing culture

- Immigration (change in geography)
- Cultural change in place (cultural orientation)



Measuring ancestry and ethnicity

Cognitive anthropology: defining culture in relation to cognition

- **Tomasello (1999)**
 - Culture is a fundamental feature of human existence based on an innate predisposition in humans
 - Cultural evolution (change) is a more potent force than genetic evolution in changing human lives
- **Nisbett (2002)**
 - Cultural practices engender and sustain specific cognitive processes which in turn perpetuate specific cultural practices

Is there assessment of culture as an explanatory factor in representative cohort studies of dementia risk?

- **Only two representative population-based cohort studies of dementia risk have included explicit measures of culture**
 - **Sacramento Area Latino Study on Aging**
 - **KAME (Japanese in Seattle)**
- **Measures: migration, language, time in country, diet, social patterns of friendship, generations since immigration, bicultural flexibility, socioeconomic consequences of migration...**
- **Issues: appropriateness of cognitive assessment is not only an issue of language, best techniques for translation?**

Existing evidence for differences in dementia risk by ancestry, culture or ethnicity: North American cohort studies

❖ **Mexicans:**

- ❖ **Sacramento Area Latino Study on Aging**
- ❖ **CUPA project (Mexico City)**

❖ **African Americans**

- ❖ **Indianapolis**
- ❖ **Chicago**

❖ **Various ancestries:**

- ❖ **European Americans, Caribbean Hispanics and African Americans in North Manhattan**

❖ **Asian**

- ❖ **Hawaiian Japanese:**
- ❖ **KAME study**

❖ **Studies of European ancestry populations**

- ❖ **Cardiovascular Health Study**
- ❖ **Pennsylvania**
- ❖ **Chicago**
- ❖ **Seattle**
- ❖ **Utah**

Differences in dementia incidence rates within North America by ancestry or ethnicity

| White/ Study location | Incidence rates per 1,000 py |
|----------------------------------|---|
| Pennsylvania | 19.3 |
| Utah | 25.5 |
| Seattle | 20.3 |
| NYC | 30.8 |
| Chicago | 24.7 |

| Ancestry | Incidence rate per 1,000 py |
|--------------------|--|
| African Am. | 29.5 - 32.2 |
| Mexican Am. | 12.0 |
| Mexican* | 20.9 |
| Caribbean | 19.0 |
| Asian Am. | 18.4 |

* Severe cognitive impairment

North American variability in dementia risk

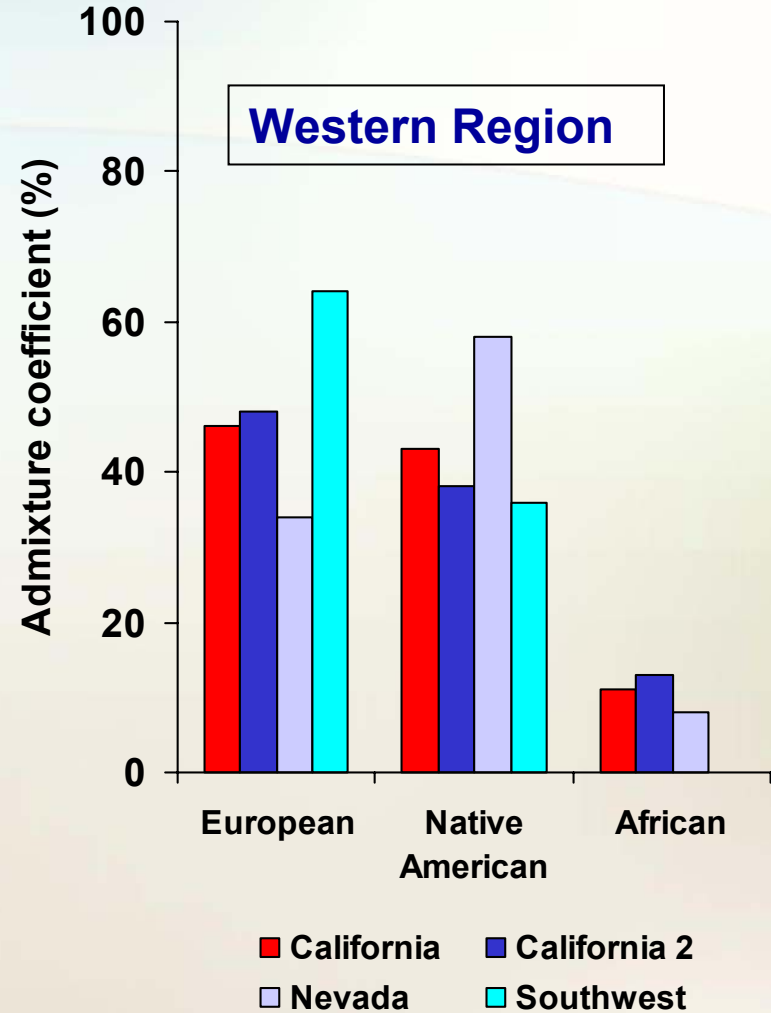
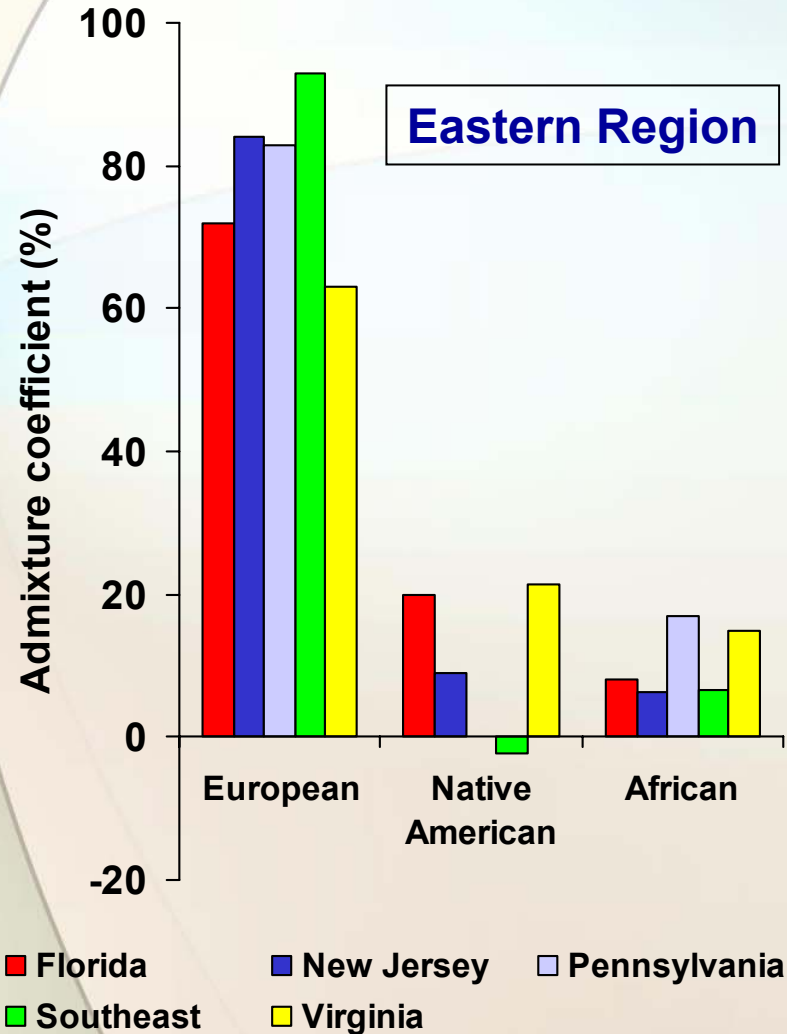
- **Within European ancestry populations there is important variability in dementia risk related to place and methodological differences**
- **The more limited studies of other ancestry/ethnic groups suggest variability within and between ethnic groups**
- **What's missing?**
 - **Population based research on Native Americans, South/east Asians, other groups**
 - **Effects of immigration on risk...**

Ancestry and dementia risk

Some issues in measuring ancestry

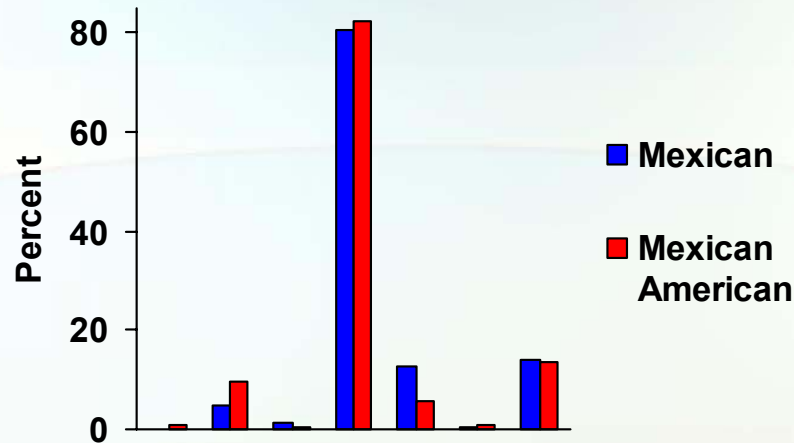
- **Population stratification within an ‘ancestral/ethnic group’**
- **Admixture as a measure of ethnicity?**
 - **Health effects may reflect consequences of societal reaction to phenotype rather than as marker of underlying genetic factors**
 - **Genetic predisposition to disease \neq admixture**
- **Interactions between genetic factors and cultural factors**
- **Changes in culture related to migration & adaptation that modify disease risk within a group thought to be homogeneous genetically**

Example of population stratification: Admixture among US 'Hispanics' by Region (based on 6 loci) (Bertoni 2003)



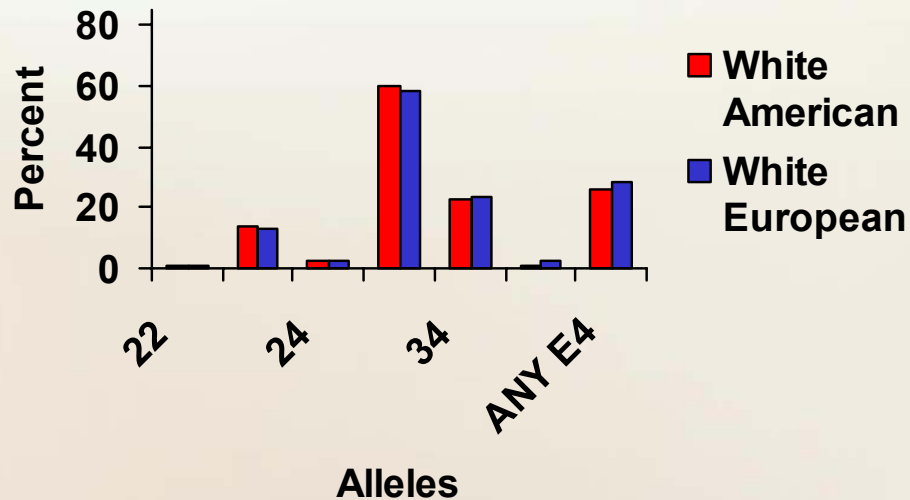
Differences in ApoE distribution by Mexican or European ancestry and country of residence

Anye4:
14.2
13.4



E4: explains <10% of dementia cases in SALSA

Anye4:
25.9
28.4



Does ApoE4 influence dementia risk equally in all population groups?

What may modify effects of APOE4 on dementia risk across diverse populations?

- **Socioeconomic and cultural factors**
- **Early life factors such as immigration, poverty, nutrition**
- **Vascular processes (atherosclerosis, lipids, metabolic, inflammatory and immune response)**
- **Other genetics factors such as PPAR α**

Sacramento Area Latino Study on Aging (SALSA)

Cohort study:

**Representative population based
sample from Sacramento,
California area**

Who:

1,789 Latinos aged 60+,

85% Mexican American

15% Central American +

60% < 9th grade education

50% were born in Mexico

Birth cohort: 1900-1935

Baseline: 1998-99

Followup: 1999-2008

Primary Goals:

**Study of cognitive decline and
dementia incidence**

Metabolic and vascular factors

**Socioeconomic status, Nativity,
immigration, cultural factors**

**Genetic factors (ApoE, PPARs,
HT genes, Psych etc)**

**Infections, stress markers,
inflammation**

Imaging (MR, PET) substudies

Study numbers and retention

| | | |
|--------------------------|-------------|---------------|
| Original cohort: | 1789 | |
| Deaths: | 362 | 20.0% |
| Refusals | 233 | 13.0% |
| Lost to follow-up | 90 | 5.0% |
| Remaining | 1104 | 77.4%* |

* Of those still alive

**SALSA: Diagnosis of dementia and cognitive impairment without dementia:
algorithm for incidence case ascertainment: Five year incidence data**

| | | | |
|--|-----------------|-----------------------------|------------------|
| Phase 1 Screening with 3MSE or SEVLT | Examined | <u>Met criteria*</u> | |
| | 1392 | <u>Yes</u> | <u>No</u> |
| Phase 2 Neuropsychological battery | Examined | 592 | 800 |
| | 484 | <u>Met criteria</u> | |
| Phase 3 Diagnosis and Case Adjudication | Examined | Yes | No |
| | 129 | 134 | 350 |
| Phase 4 Final diagnosis | Examined | <u>Demented/CIND</u> | |
| | 120 | Yes | No |
| | | 120 | 9 |
| | | <u>Demented</u> | CIND |
| | | 74 | 46 |
| *Test LE 20 percentile or: 3MSE decline GE 8 or SEVLT decline GE 3 | | | |

Socioeconomic status and cultural factors in Sacramento Area Latino Study on Aging participants by country of birth

| Nativity | Mexico | US |
|--|--------------|----------------|
| <u>Not Attended School</u> (%) | 20% | 6%** |
| Mean years of education | 5.0 | 10.0*** |
| Income (%<\$1k per month) | 60% | 30%** |
| Own home (% yes) | 56% | 78%** |
| Spanish speaking only (% yes) | 88.6% | 26%*** |
| Cultural orientation score (mean) | 13.6 | 31.0*** |

SALSA 21-point cultural orientation scale

Do you speak Spanish?

Do you speak English?

Do you prefer to speak Spanish/English?

Do you associate with Anglos?

Do you associate with other Mexicans and /or Latinos?

Language preferences for media

Reading and writing preferences by language

Do think in English/Spanish?

Do you travel to Mexico or to another Latin American country?

Childhood friends Latino/Anglo?

Present friends Latino/Anglo?

Does your family cook Mexican/Latino foods?

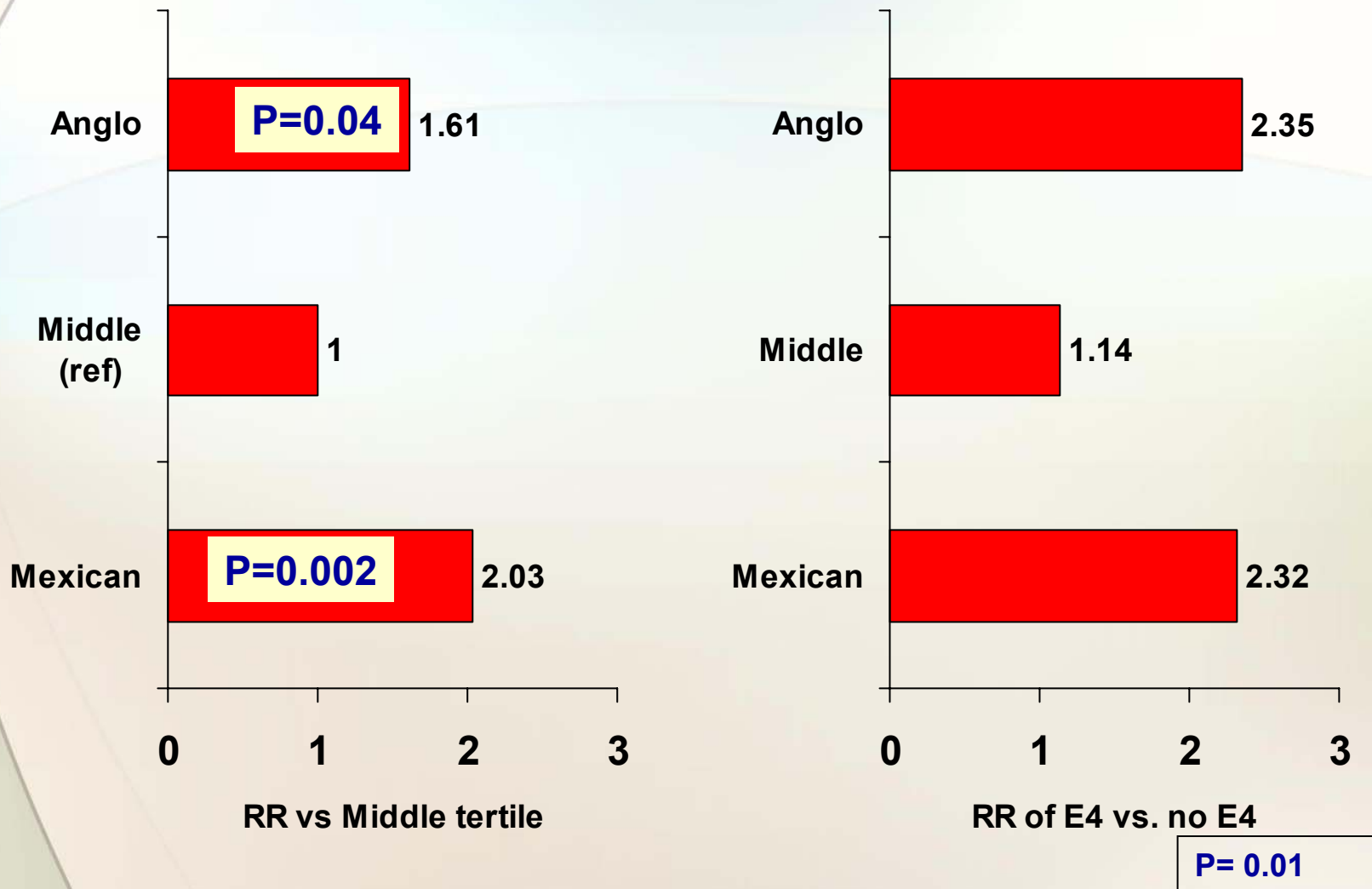
Do you identify yourself as Latino/Anglo?

How often do you talk on the phone to friends or relatives in Mexico or other Latin American countries?

Scale properties by nativity

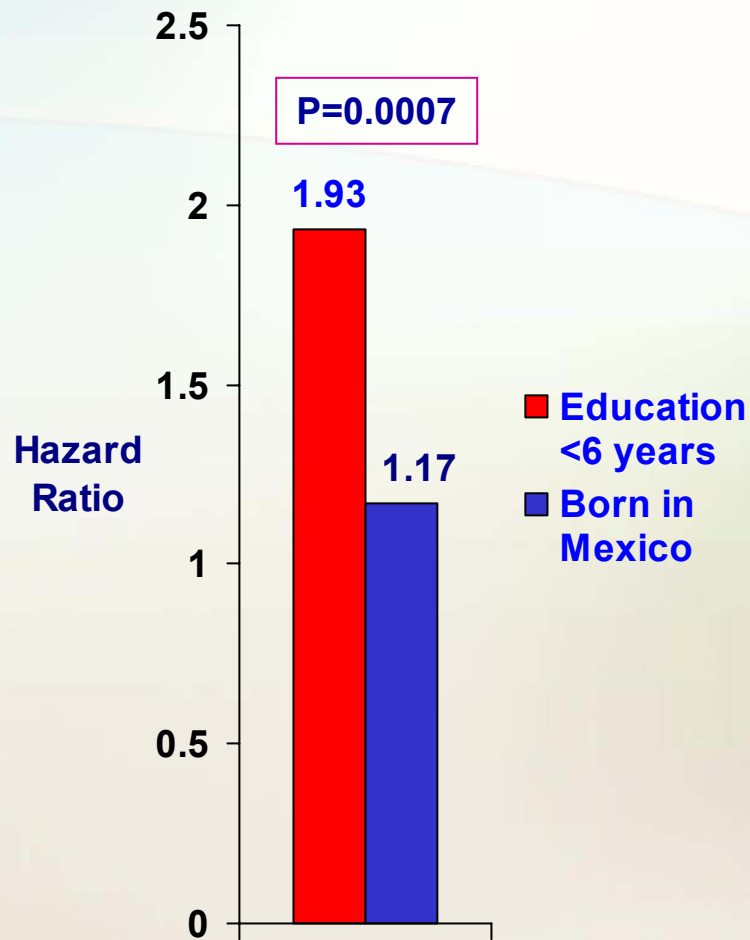
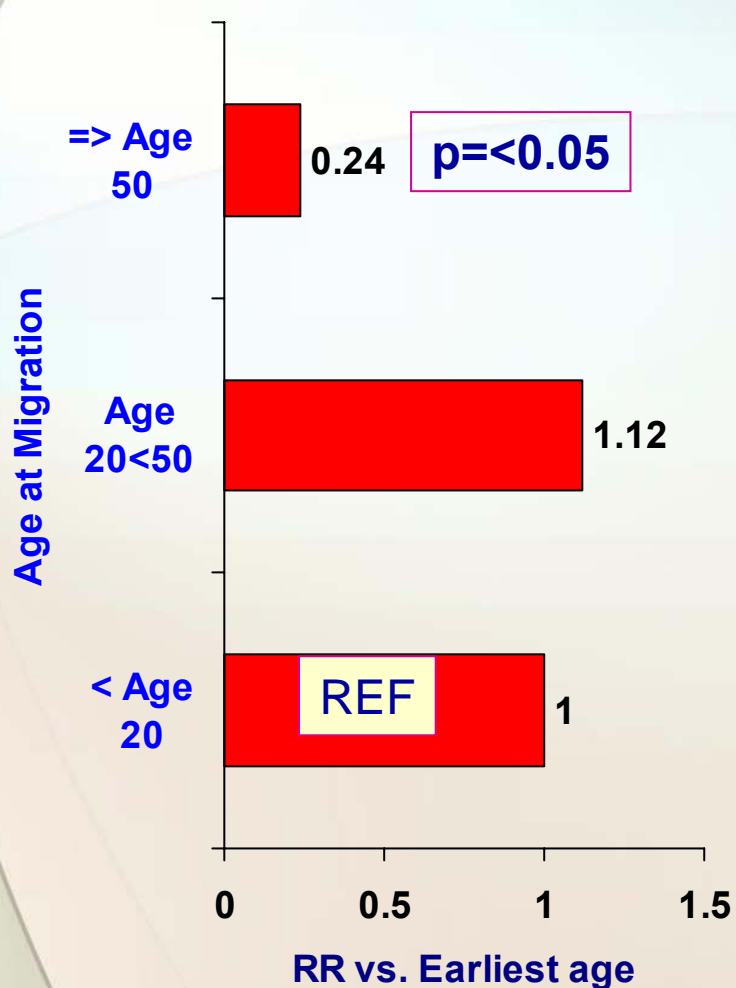
| | Mexico | US |
|--------|--------|------|
| Mean | 13.6 | 30.9 |
| SD | 9.4 | 9.9 |
| Median | 10.0 | 32.0 |
| Range | 0-54 | 3-56 |
| Alpha | 0.88 | 0.87 |

Cultural orientation is associated with dementia/CIND rates overall which is modified by E4 status in the SALSA (proportional hazards models)



Later age at migration from Mexico is associated with lower risk of dementia/CIND in SALSA participants who were born in Mexico

Low education is associated with higher risk

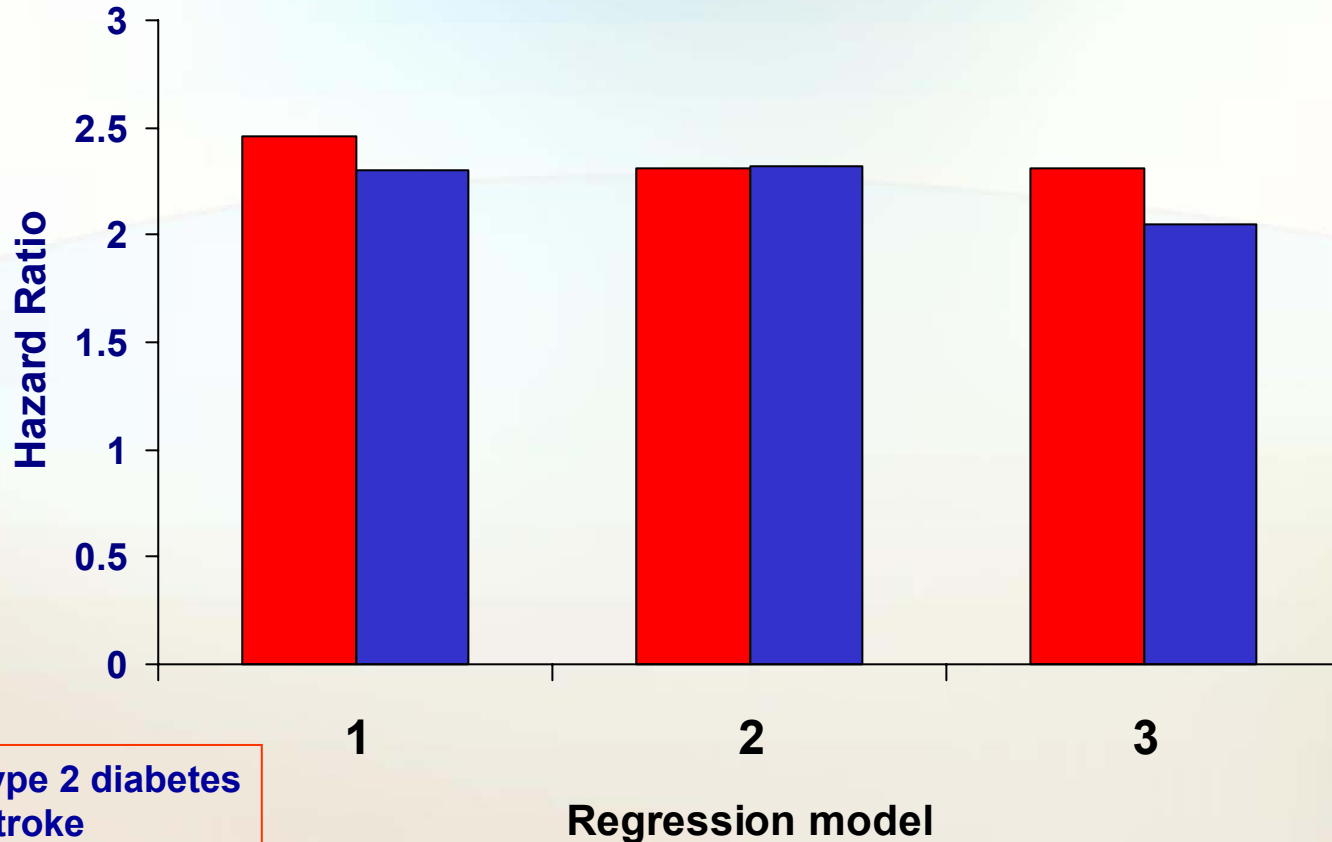




Vascular and metabolic factors and risk of dementia

Risk of dementia by exposure to risk factors

Hazard ratios for incidence of dementia/CIND associated with baseline stroke or type 2 diabetes from a series of proportional hazards models in SALSA



32% with type 2 diabetes
16% with stroke

■ Type 2 diabetes ■ Stroke

1- Unadjusted

2- age, education

3 age, education, gender, waist circumference, DM treatment

Genetics of type 2 diabetes and dementia? PPAR-Regulated Inflammatory Markers

PPAR α

- C-reactive protein
- Endothelin-1
- Fibrinogen
- IL-6

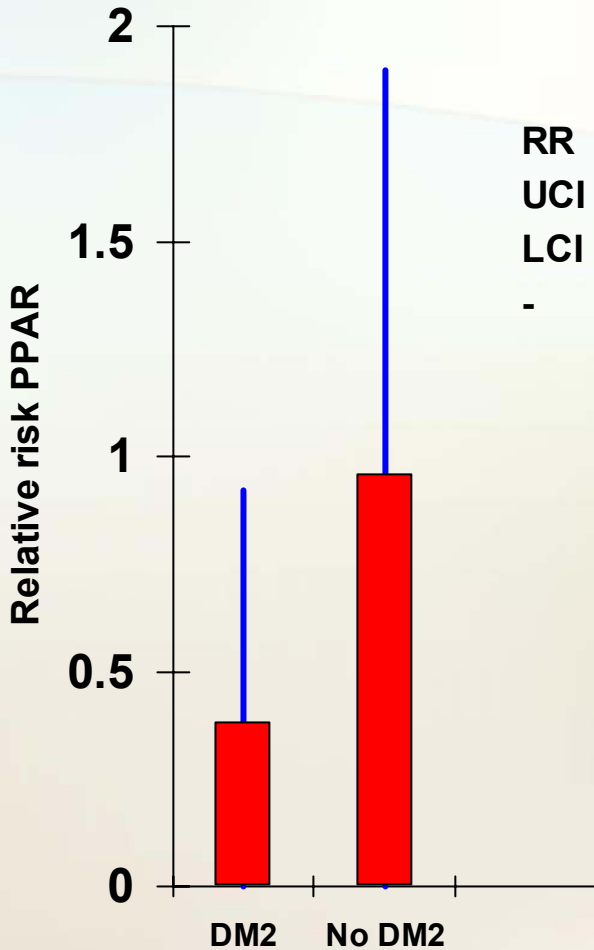
PPAR γ

- C-reactive protein
- Matrix metalloproteinase-9
- Plasminogen activator inhibitor-1
- TNF- α

Risk of dementia/CIND in relation to PPAR-gamma by type 2 diabetic status

PPAR- gamma Pro 12Ala influences

- Diabetes
- Obesity
- Metabolic function
- Coded as:
 - CC (1) vs. CG+GG (0)

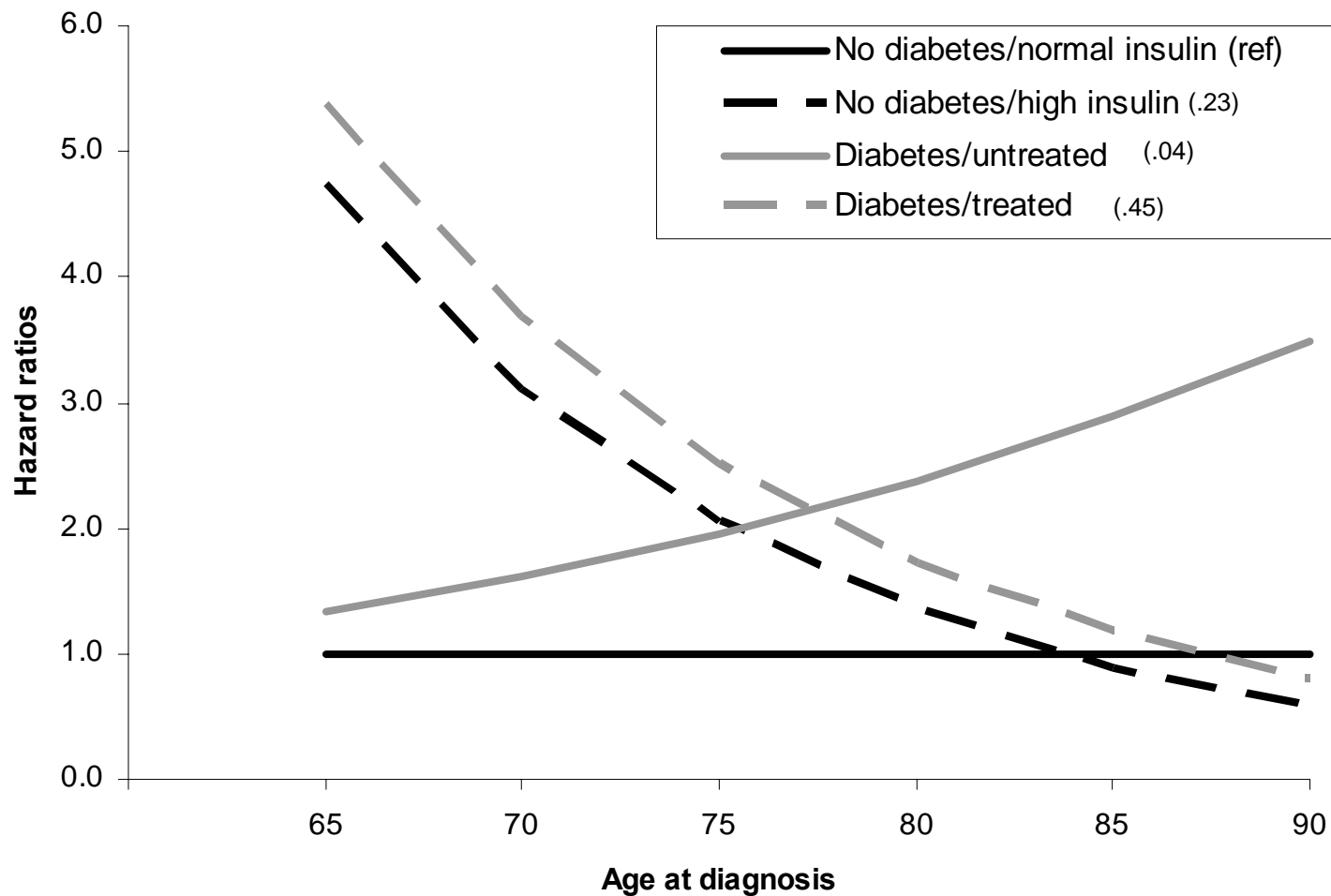


From a logistic regression model including PPAR, age, gender and fasting glucose

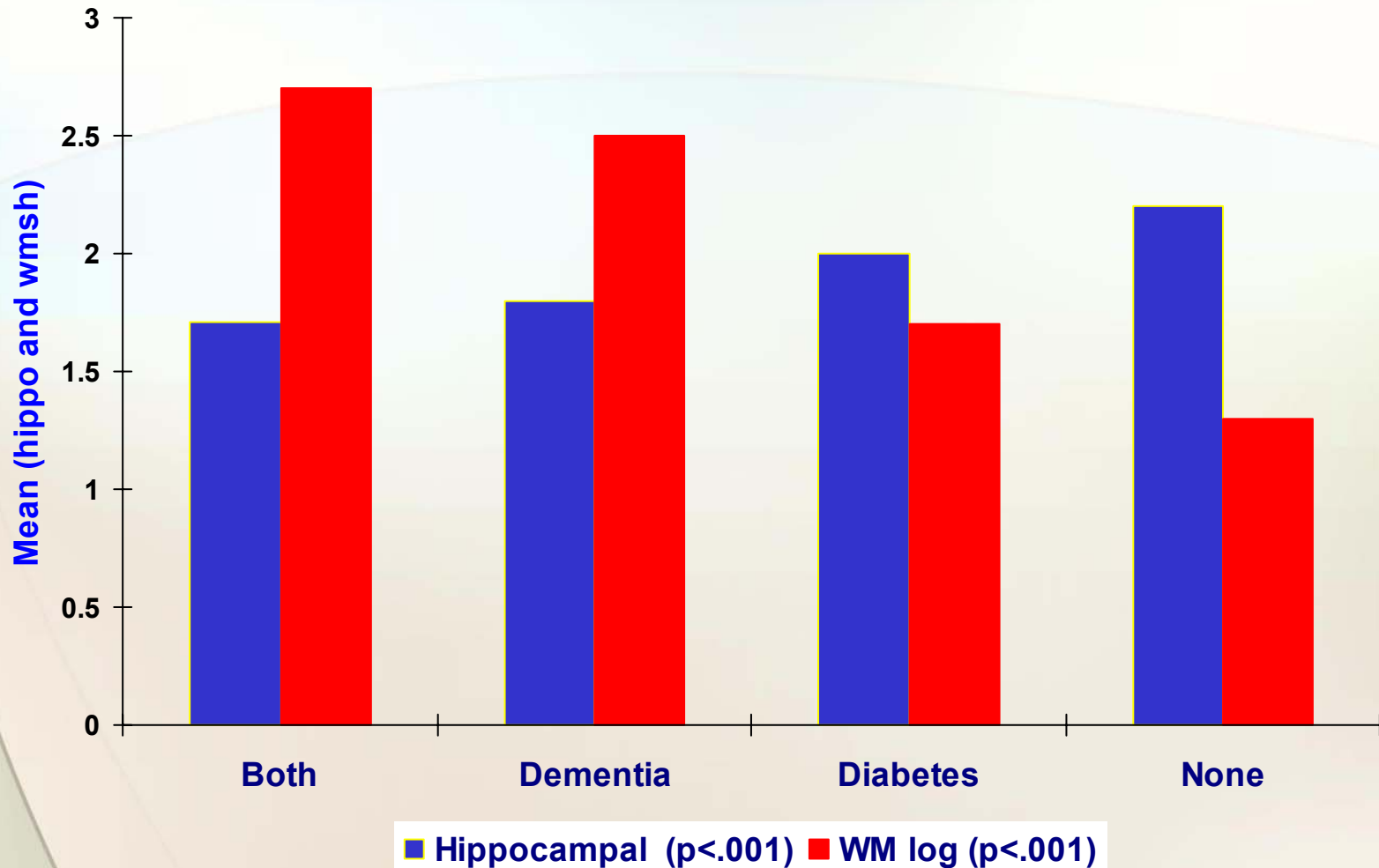
Insulin and dementia in SALSA

- **Examine risk by**
 - **High vs. Low insulin in non-Diabetics and Diabetics**
 - **Effects of insulin treatment in Diabetics**
- **Analyses with proportional hazards model including adjustments for APOE, BMI, age, gender**

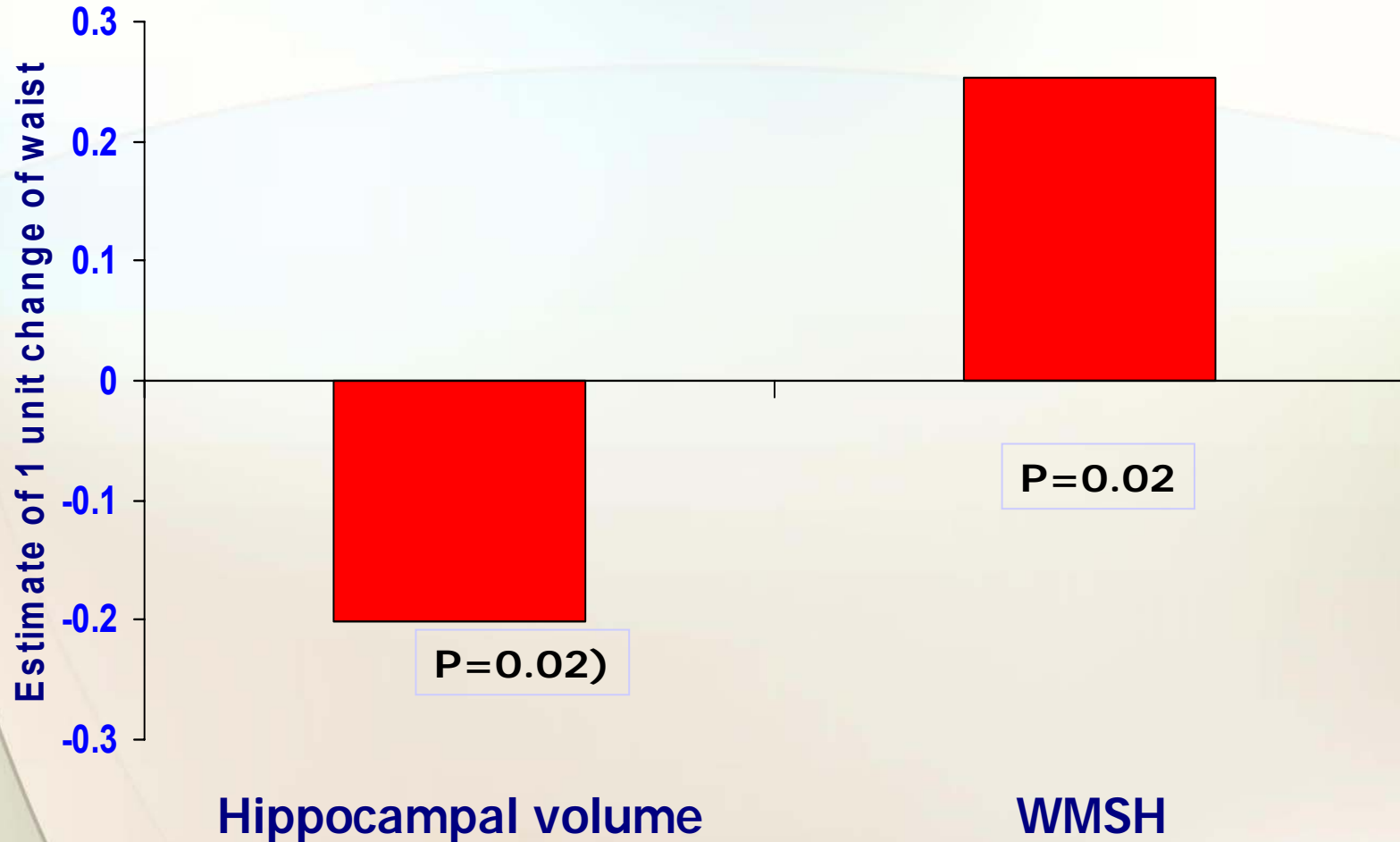
Rates of Dementia/CIND and insulin from a proportional hazards (survival) model



Hippocampal atrophy and white matter (WM) hyperintensities are greater among those with both diabetes and dementia/CIND or dementia/CIND alone vs. diabetics or normals in SALSA imaging subsample



Does obesity directly affect the brain? Central obesity (waist) and aging brain (SALSA imaging subsample)



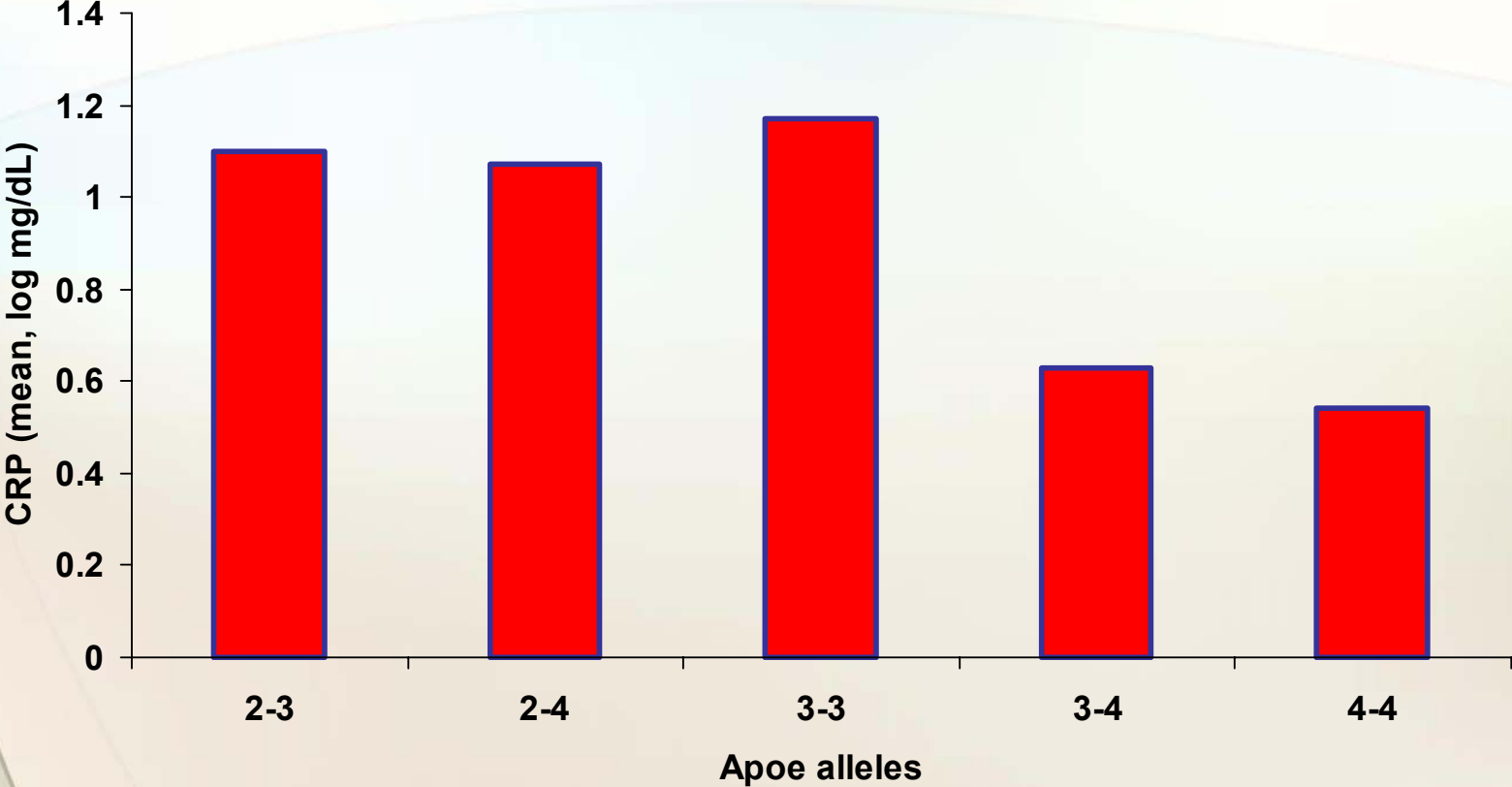
Vascular, immune and metabolic pathways

- **Homocysteine and B-vitamins**
- **C-reactive protein**

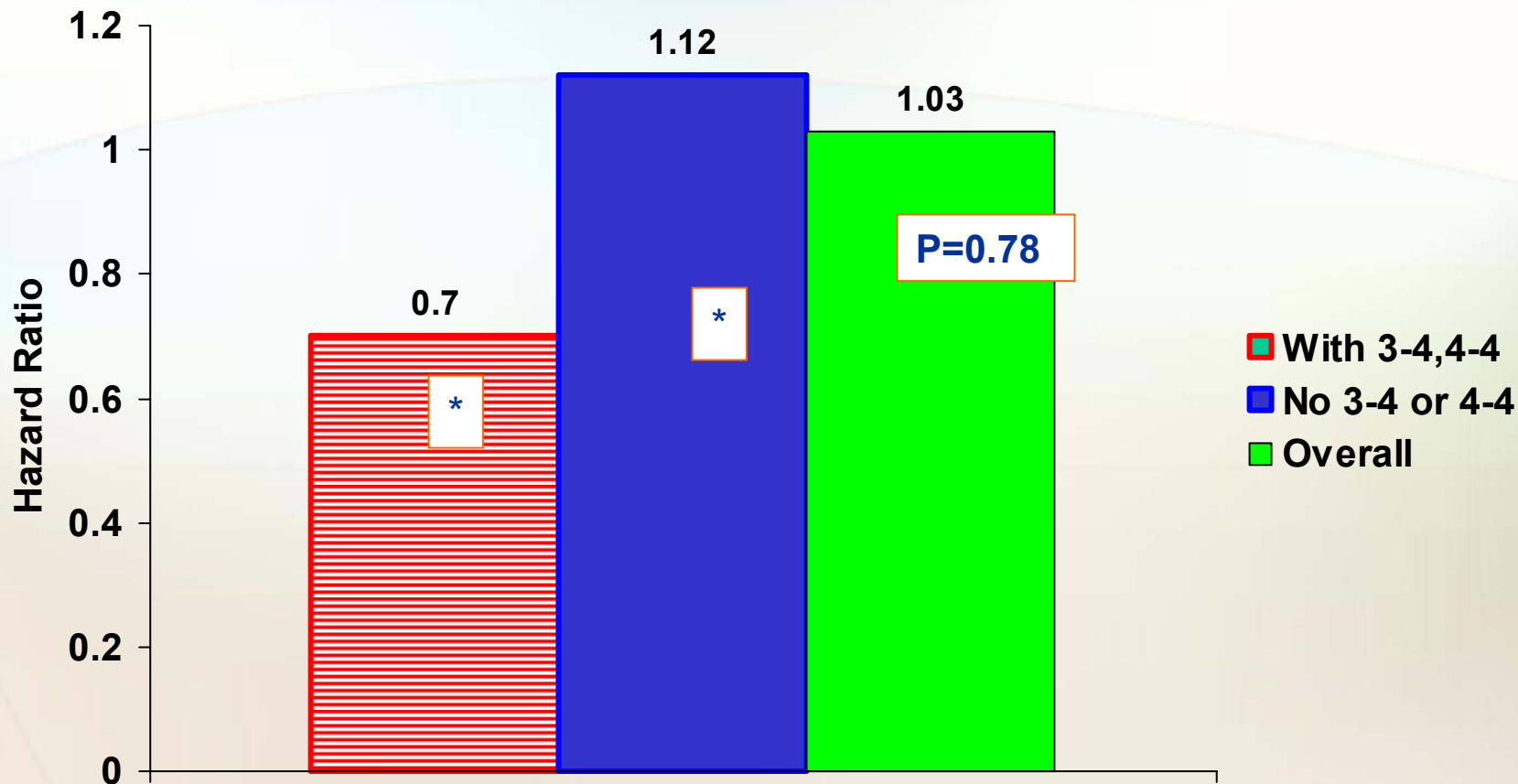
Hazard ratios for incident dementia and CIND in relation to *homocysteine* (log) from a series of proportional hazards models using age at diagnosis or censoring as time variable.

| | Model 1 | Model 2 | Model 3 | Model 4 |
|-------------------|---------------------------|---|---|--|
| | Hazard Ratios (CI) | | | |
| HCY (log) | 1.58 (0.88-2.83) | 2.52(1.17-5.45) | 1.83 (0.81-4.13) | 2.39 (1.11-5.16) |
| Covariates | None | SQRT Plasma B12, Log RBC folate, Log GFR | Model 2 + baseline stroke, education | Model 2+ Education Excluding stroke |

High sensitivity c-reactive protein at baseline is lower in those with APOE 3-4 or 4-4 from a GLM model (age adjusted) (p<0.0001)



HS-CRP in 3-4,4-4 group is associated with a lower rate of dementia/CIND
HS-CRP is not associated with dementia/CIND overall



*** P value for APOE*CRP interaction term=0.04**

Current projects

- **Insulin degrading enzyme**
- **PPARs and other genetic factors**
- **Evaluation of central autonomic neuropathy and dementia/CIND (portable ECGs)**
- **Cortisol variability in relation to cognitive decline and dementia incidence**
- **Evaluation of multilevel effects of census tract residence on dementia, mortality, cognitive decline, incidence of diabetes, and biochemical pathways (CRP, IL6)**
- **Assessment of imaging data using new spatial techniques**

Current projects

- **Inflammatory and immune response pathways**
- **Evaluating infectious agents in relation to dementia risk**
 - **CMV, HSV1 & 2**
 - Aiello et al JAGS, 2006
- **Initiating proposal for study of intergenerational risks for dementia**
 - **Children (age ~ 50)**
 - **Grandchildren (age ~30)**