Dementia & Alzheimer’s Research in Puerto Rico

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Chair, Department of Medicine
School of Medicine
University of Puerto Rico

29st ADI International Conference, San Juan, PR May 2, 2014
Puerto Rico
Agenda

- **Puerto Rico**
  - Geographics & Demographics
  - **Genetic Influence Familial Study (2002-2014)**
    Columbia University / Sergievsky Center
    - LOAD
    - EOAD
  - **10/66 Dementia Cohort Study (2006-2014)**
    Institute of Psychiatry, London, UK
    - Prevalence Phase - \( N = 2,000 \)
    - Incidence Phase - \( N = 1,265 \)
Caribbean island conquered by the Spanish - 1492
After the war - became part of USA - 1898
  Commonwealth - 1950
Population - 3.7 million people
  14 % over 65 y/o
Principal language - Spanish
  Second language - English
Pirámide Poblacional de Puerto Rico (2005)

Fuente de los datos: Encuesta de la Comunidad 2005. US Census Bureau
Alza en muertes por el Alzheimer

La enfermedad pasó de la decimocuarta a la quinta causa de fallecimientos

LIBRA SANJURO MÉNDEZ Para Primera Hora

A PRONAR de que las muertes por Alzheimer han incremecido al punto de que la tasa de mortalidad en las islas es más alta que en Estados Unidos, los rasgos para este asunto son desconocidos, según el director del Centro para el Estudio Interdisciplinario de Enfermedades Neurodegenerativas en Puerto Rico, el prof. Raúl Gómez. En el primer año, la tasa de muertes asociadas al Alzheimer es más alta que en el segundo año, aumentando de 1.3 al 1.31. Este incremento ha llevado a los expertos a sugerir que el Alzheimer de la decimocuarta (1999) a la quinta (2000) posición entre las causas de muerte más comunes en el país.

El Alzheimer es un padecimiento progresivo que afecta, por lo general, a personas mayores de 65 años y con 10-15% de personas mayores de 85 años. Con menos del 5% de los mayores de 65 años y alrededor de 20% de los mayores de 85 años, la enfermedad afecta a más de 4,000 personas en Puerto Rico y a más de 4,000 personas en los Estados Unidos.

Enfermedad neurologica

El Alzheimer es un padecimiento progresivo que afecta, por lo general, a personas mayores de 65 años.

CIFRA

GASTOS

$1,500

Cantidad mínima de dinero que pueden llegar a costar los tratamientos y atender a los pacientes.
Primary mortality causes - PR

- 1- Heart disease
- 2- Cancer
- 3- Diabetes Mellitus
- 4- Alzheimer’s disease
“ENFERMEDAD FAMILIAR INFLUENCIA GENETICA ALZHEIMER” (EFIGA)

Genetic Influence Family Study
LOAD / EOAD
History

- 1989 - Studying Latino families - in NY.

- Found double risk in Caribbean patients - PR, DR
  - Islands considered geographic isolates
  - Migration predominantly out of country

- No risk factors could explain differences in disease rates

- PSEN1, PSEN2, SORL1
Since June 2002, a cohort of Caribbean Hispanics from PR with familial late and early-onset AD have been studied, after IRB approval was obtained.

Identified, examined and collected blood samples from > 1,300 individuals of > 350 families affected with the disease.

Studies done at the Clinical Research Center, University Hospital, Puerto Rico Medical Center, or at patient’s homes.
EFIGA Research Study

- Neuropsychological Evaluation
- Physical/ Neurological Examination
- Blood tests, genetic testing and APO-E
- Socio-Demographic and Risk Factor Interview
- Clinical Interview
- Informant Interview (if applicable)
Neuropsychological Tests

Memory
- Selective Reminding Test
- Benton Recognition

Orientation Test

Language
- Boston Naming
- Control Fluency Letter
- Category Fluency Test
- Sentence Repetition
- Comprehension

Abstract Reasoning
- Similarities
- Identities/Oddities

Construction
- Rosen Figure Test
- Benton Matching Test

Attention
- Cancellation Test
  (Shape/TMX)
Early Onset Familial Genetic Study

- 2007 - 2014 - largest cohort of EOAD
- > 150 families identified in PR
  - 15 % - 40 - 49 yrs
  - 53.7 % ages 50 - 59 yrs
- 40 % PSEN1
- 100% carriers have Gly206Ala mutation
- West side more clusters - common ancestor
- Study ongoing
Gly206Ala mutation:
- Associated with a mean age of onset of 56 years, ranging from 47 years to as late as 70 years.

Presentation:
- Increased seizures
- Increased hallucinations

Fully penetrant

Age at onset is not modified by ApoE genotype
Identification of Novel Loci for Alzheimer Disease and Replication of CLU, PICALM, and BIN1 in Caribbean Hispanic Individuals

Arch Neurol. Nov 8, 2010


Cheng, Barral, Reitz, Lantigua, and Mayeux), Gertrude H. Sergievsky Center (Drs Lee and Mayeux), and Departments of Neurology (Drs Barral, Reitz, and Mayeux), Psychiatry (Dr Mayeux), and Medicine (Dr Lantigua), College of Physicians and Surgeons, and Department of Epidemiology, School of Public Health (Drs Lee and Mayeux), Columbia University, New York, New York; Universidad Tecnológica de Santiago, Santiago, Dominican Republic (Dr Medrano); Department of Internal Medicine, University of Puerto Rico School of Medicine, San Juan, Puerto Rico (Dr Jiménez-Velázquez); Centre for Research in Neurodegenerative Diseases, Departments of Medicine, Laboratory Medicine and Pathobiology, and Medical Biophysics, University of Toronto, and Toronto Western Hospital Research Institute, Toronto, Ontario, Canada (Drs Rogaeva and St. George-Hyslop); and Cambridge Institute for Medical Research and Department of Clinical Neurosciences, University of Cambridge, Cambridge, England (Dr St. George-Hyslop).
Family

Exome Selected Individuals
230-21  Age of onset = 47
230-24  Age of onset = 70
Age at onset varies widely

Exome Selected Individuals
458-5  Age of onset = 43
458-52 Age of onset = 64
El Velorio (Baquiné) de Francisco Oller
Early Onset AD

- Descriptive profile  N = 147 individuals affected with the Early Onset Alzheimer’s disease in Puerto Rico (Gly206ala mutation)
EOAD in PR

Individual’s Gender

- Female: 58%
- Male: 42%

N = 147
EOAD in PR

Age Group

- 40-49: 15%
- 50-59: 54%
- 60-65: 31%
EOAD in PR

Marital Status

- Married: 67.3%
- Widowed: 13.6%
- Never Married: 2.7%
- Divorced: 14.3%
- Separated: 2%
EOAD in PR

Education Level

- Some: 17.1%
- Primary: 6.2%
- Middle: 13.7%
- Secondary: 27.5%
- College: 18.6%
- > College: 7.6%
EOAD in PR

Occupation

- Housewife: 15.1%
- House & Other: 3.4%
- Unskilled & Semiskilled: 18.5%
- Skilled Trade: 14.4%
- Office Work: 9.6%
- Manager Business: 9.6%
- Professional/Technical: 28.1%
- Other: 1.4%
EOAD in PR

First Symptom

- Memory: 74.8%
- Performance: 0.7%
- Language: 0.7%
- Disorientation: 5%
- Personality Change: 5.8%
- Depressed Mood: 6.5%
- Behavior Mood: 2.9%
- Psychosis: 3.6%
Toxic Habits

- Alcohol Use: 19%
- Smoking: 27%
- Illicit Drug: 3%
APOE*4 in Puerto Rico

Allele Frequency PR

- 3,3 (54%)
- 3,4 (32%)
- 4,4 (7%)
- 2,4 (3%)
- 2,3 (4%)
- 4,4 (7%)
APOE*4 in Dominican Republic
### Number of Individuals affected with the Early Onset Alzheimer Disease

<table>
<thead>
<tr>
<th>Northern Region</th>
<th># Individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carolina</td>
<td>30</td>
</tr>
<tr>
<td>Camuy</td>
<td>26</td>
</tr>
<tr>
<td>Vega Baja</td>
<td>13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Southern Region</th>
<th># Individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coamo</td>
<td>15</td>
</tr>
<tr>
<td>Ponce</td>
<td>11</td>
</tr>
<tr>
<td>Yauco</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Eastern Region</th>
<th># Individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caguas</td>
<td>60</td>
</tr>
<tr>
<td>Barranquitas</td>
<td>23</td>
</tr>
<tr>
<td>San Lorenzo</td>
<td>19</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Western Region</th>
<th># Individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayaguez</td>
<td>41</td>
</tr>
<tr>
<td>Aguadilla</td>
<td>27</td>
</tr>
<tr>
<td>Isabela</td>
<td>17</td>
</tr>
</tbody>
</table>

N=396
Acknowledgments

Genetic Study

Funding:
- Columbia University-NIH
- Fidelity Foundation

Health Innovation Award
Best Clinical Investigation
Merck Co., Sept. 2009

EFIGA/EOAD members:
- Richard Mayeux, MD - PI-NY
- Rafael Lantigua, MD
- Martin Medrano, MD
- Joe Lee, PhD
- Vincent Santana, MS
- Maribella Gonzalez, PhD
- Lydia Robles, MS
- Aleyda Maldonado, Ph.D
- Ivonne Z. Jiménez, MD-PI-PR
The Next Steps – DIAN Study - 2014

- The Dominantly Inherited Alzheimer Network (DIAN) – Prevention Trial
- International research partnership of leading scientists determined to understand a rare form of Alzheimer’s disease that is caused by a gene mutation.
- Understanding of this form of Alzheimer's disease may provide clues to decoding other dementias and developing dementia treatments.
More and more studies suggest that *lifestyle* changes may be able to silence the expression of risk genes, a phenomenon called *epigenetics*.
The 10/66 Puerto Rico Dementia Prevalence Study
Prevalence studies worldwide

- **Regions well covered with several studies of good methodological quality**
- **Some studies but insufficient to derive regional estimates with confidence**
- **Single epidemiological studies**
- **No epidemiological studies**
Bayamón, Puerto Rico
10/66 research studies

- Doorknocking at catchment area
- Cognitive test
- Clinical interview
- Socio-demographic and risk factor interview
- Physical/ neurological examination
- Blood tests
- Informant interview
10/66 Puerto Pico Prevalence Study-Data
December 2006 - June 2009
Participant’s Gender
N=2000

Percent

<table>
<thead>
<tr>
<th>Gender</th>
<th>Percent</th>
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</thead>
<tbody>
<tr>
<td>Male</td>
<td>32.1%</td>
</tr>
<tr>
<td>Female</td>
<td>67.9%</td>
</tr>
</tbody>
</table>
Participant’s Age Group

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>65-69</td>
<td>21%</td>
</tr>
<tr>
<td>70-74</td>
<td>23%</td>
</tr>
<tr>
<td>75-79</td>
<td>24%</td>
</tr>
<tr>
<td>80+</td>
<td>32%</td>
</tr>
</tbody>
</table>
Participant’s Marital Status

- Never Married: 6.2%
- Married/Cohabiting: 48.6%
- Widowed: 33.4%
- Divorced/Separated: 11.9%
Participant’s Occupation

- Retired: 65.0%
- Housewife/househusband: 31.9%
- Full Time Work: 1.7%
- Part Time Work: 1.1%
- Unemployed (looking for work): 0.2%
Participant’s Level of Education

- None: 2%
- Some (did not complete primary): 13%
- Completed Primary: 19%
- Completed Secondary: 39%
- College: 27%
Participant’s Daily Habits

Physical Activity

- Physical Active: 18%
- Fairly Active: 42.6%
- Not Very Active: 26.7%
- Not at all: 12.7%

Smoking

- No: 82.7%
- Yes: 17.3%
Have you ever been a heavy drinker???
Participant’s Nutrition/Dietary Findings

Frequency of Hunger Through Shortage of Food

- Never: 99%
- Some Days: 1%

Frequency of Eating Meat and Fish

- Never: 4.9%
- Some Days: 22.1%
- Most Days: 22.4%
- Every Day: 18.1%

Servings of Fruit and Vegetables in the last 3 days

- 0 servings: 8.9%
- 1-2 servings: 14.9%
- 3-4 servings: 34.4%
- 5-6 servings: 32.9%
- 7 servings: 0.8%
- 8-10 servings: 4.8%
- 11 servings: 0.2%
Participant’s Household Characteristics

Water in household

Plumbed bathroom in household
Participant’s Health Findings

- High Blood Pressure: 69.2%
- Diabetes: 43.3%
- Heart Problem: 25.3%
- Stroke: 8.5%
Frequency of Participants with Private Insurance

- 95.80% yes
- 4.20% no
Participant’s Need for Care

- Needs Care Some of the Time: 4.9%
- Needs Care Much of the Time: 9.9%
- Does Not Need Care: 85.3%
Participant’s social network typology

- Family dependent: 16.70%
- Locally integrated: 54%
- Locally self-contained: 11%
- Widder community focused: 10%
- Private: 9%
## Prevalence of Dementia Case Identification

N=1926/2000

<table>
<thead>
<tr>
<th></th>
<th>DSM IV Dementia Diagnosis</th>
<th>Education Adjusted 10/66 Lancet Dementia Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Case</td>
<td>95.4%</td>
<td>88.3%</td>
</tr>
<tr>
<td>Case</td>
<td>4.6%</td>
<td>11.7%</td>
</tr>
</tbody>
</table>
Prevalence of 10/66 and DSM IV Dementia

Rodriguez et al, Lancet 2008
**Prevalence of Depression Case Identification**

<table>
<thead>
<tr>
<th></th>
<th>ICD 10 Depressive Diagnosis</th>
<th>DSM IV Depression Diagnosis</th>
<th>GMS/AGECAT Depression Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case</td>
<td>1.8%</td>
<td>.8%</td>
<td>22.1%</td>
</tr>
</tbody>
</table>

PR data from December 2006 through July 2008

<table>
<thead>
<tr>
<th>Past History of Depression</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>21.5%</td>
</tr>
<tr>
<td>No</td>
<td>78.5%</td>
</tr>
</tbody>
</table>
### Prevalence of Dementia Case Identification 08

<table>
<thead>
<tr>
<th></th>
<th>CSI’D cognitive Score</th>
<th>CSI’D Discriminant Function Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non - Case</td>
<td>64.3%</td>
<td>86.3%</td>
</tr>
<tr>
<td>Possible Case</td>
<td>12.2%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Probable Case</td>
<td>23.4%</td>
<td>11.6%</td>
</tr>
</tbody>
</table>

PR data from December 2006 through July 2008

<table>
<thead>
<tr>
<th></th>
<th>Lancet 10/66 Dementia Diagnosis</th>
<th>Education Adjusted Lancet 10/66 Dementia Diagnosis</th>
<th>DSM IV Dementia Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Case</td>
<td>88.9%</td>
<td>88.4%</td>
<td>94.2%</td>
</tr>
<tr>
<td>Case</td>
<td>11.1%</td>
<td>11.6%</td>
<td>5.8%</td>
</tr>
</tbody>
</table>

PR data from December 2006 through July 2008

<table>
<thead>
<tr>
<th></th>
<th>Family History of Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>20.2%</td>
</tr>
<tr>
<td>No</td>
<td>78.8%</td>
</tr>
</tbody>
</table>
Puerto Rico 10/66 Incidence Study (2011-2013)
• Baseline cohort (N=2000) interviewed 2006-2009 - revisited

• Follow-up (2011-2013)
  – Re-interviewed 1268 (63.1%)
  – Deceased 299 (14.9%)
  – Refused/ not traced 442 (22.0%)
  – 6327 person years of follow-up

• Dementia free cohort (n=1765)
  – 1388 (88.7%) follow-up to death or re-interview
  – 5509 person years of follow-up
Incidence of 10/66 Dementia and DSM-IV dementia (per 1000 person years)

Prince et al, Lancet 2011
Puerto Rico - Incidence of 10/66 Dementia (per 1000 person years) by age and gender
Sociodemographic factors and 10/66 dementia risk

<table>
<thead>
<tr>
<th>Factor</th>
<th>10/66 (meta-analysis)</th>
<th>Puerto Rico</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 5 year band)</td>
<td>1.67 (1.56-1.79)</td>
<td>1.90 (1.55-2.34)</td>
</tr>
<tr>
<td>Gender (M vs F)</td>
<td>0.72 (0.61-0.84)</td>
<td>0.81 (0.55-1.20)</td>
</tr>
<tr>
<td>Education (per level)</td>
<td>0.89 (0.81-0.87)</td>
<td>0.90 (0.76-1.09)</td>
</tr>
<tr>
<td>Assets (per asset)</td>
<td>0.93 (0.88-1.00)</td>
<td>1.25 (0.69-2.27)</td>
</tr>
<tr>
<td>Cognitive reserve</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animal naming</td>
<td>0.93 (0.91-0.94)</td>
<td>0.88 (0.83-0.92)</td>
</tr>
<tr>
<td>Literacy</td>
<td>0.68 (0.55-0.84)</td>
<td>0.55 (0.30-1.02)</td>
</tr>
</tbody>
</table>

Prince et al, Lancet 2011
Puerto Rico 10/66 cohort study
Factors independently associated with mortality

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 5 year band)</td>
<td>1.48 (1.30-1.68)</td>
</tr>
<tr>
<td>Gender (M vs F)</td>
<td>1.38 (1.09-1.73)</td>
</tr>
<tr>
<td>Education (per level)</td>
<td>0.87 (0.79-0.96)</td>
</tr>
<tr>
<td>10/66 dementia</td>
<td>2.97 (2.27-3.87)</td>
</tr>
</tbody>
</table>
Puerto Rico 10/66 cohort study
Anaemia and 10/66 dementia risk

<table>
<thead>
<tr>
<th></th>
<th>Prevalence</th>
<th>Proportional sub-hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>32.2%</td>
<td>1.32 (0.88-1.97)</td>
</tr>
<tr>
<td>Hb</td>
<td></td>
<td>0.91 (0.71-1.04)</td>
</tr>
<tr>
<td>No anaemia</td>
<td></td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Microcytic anaemia</td>
<td>2.4%</td>
<td>1.98 (0.66-5.94)</td>
</tr>
<tr>
<td>Normocytic</td>
<td>29.1%</td>
<td>1.30 (0.86-1.97)</td>
</tr>
<tr>
<td>Macrocytic anaemia</td>
<td>0.8%</td>
<td>Too few cases</td>
</tr>
</tbody>
</table>
### Puerto Rico 10/66 cohort study
Thyroid function and 10/66 dementia risk

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Prevalence</th>
<th>Proportional sub-hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid stimulating hormone (TSH)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per SD</td>
<td></td>
<td>0.84 (0.74-0.97)</td>
</tr>
<tr>
<td>Normal TSH</td>
<td>81.7%</td>
<td>1</td>
</tr>
<tr>
<td>Sub-clinical elevation</td>
<td>5.1%</td>
<td>0.69 (0.25-1.95)</td>
</tr>
<tr>
<td>Clinical elevation</td>
<td>13.3%</td>
<td>0.52 (0.26-1.05)</td>
</tr>
</tbody>
</table>
**Puerto Rico 10/66 cohort study**  
**Micronutrients and 10/66 dementia risk**

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Prevalence</th>
<th>Proportional sub-hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vitamin B12</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per SD</td>
<td></td>
<td>1.05 (0.88-1.27)</td>
</tr>
<tr>
<td>Low B12</td>
<td>8.9%</td>
<td>0.84 (0.41-1.74)</td>
</tr>
<tr>
<td><strong>Folate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per SD</td>
<td></td>
<td>1.01 (0.83-1.23)</td>
</tr>
<tr>
<td>Low folate</td>
<td>5.3%</td>
<td>0.66 (0.20-2.12)</td>
</tr>
<tr>
<td><strong>Homocysteine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per SD</td>
<td></td>
<td>0.99 (0.81-1.21)</td>
</tr>
<tr>
<td>Normal homocysteine</td>
<td>64.2%</td>
<td>1</td>
</tr>
<tr>
<td>Mild elevation</td>
<td>33.2%</td>
<td>1.02 (0.65-1.58)</td>
</tr>
<tr>
<td>Moderate elevation</td>
<td>2.6%</td>
<td>0.76 (0.19-3.04)</td>
</tr>
</tbody>
</table>
### Puerto Rico 10/66 cohort study
#### Diabetes and 10/66 dementia risk

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Prevalence</th>
<th>Puerto Rico</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>41.2%</td>
<td>0.97 (0.66-1.43)</td>
</tr>
<tr>
<td><strong>By diabetes control</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes</td>
<td>58.8%</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Detected/ controlled</td>
<td>10.3%</td>
<td>0.87 (0.45-1.70)</td>
</tr>
<tr>
<td>Detected/ not controlled</td>
<td>21.3%</td>
<td>1.25 (0.81-1.93)</td>
</tr>
<tr>
<td>Not detected, not controlled</td>
<td>9.6%</td>
<td>0.49 (0.20-1.22)</td>
</tr>
<tr>
<td><strong>Glucose</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>per SD</td>
<td></td>
<td>1.17 (0.98-1.40)</td>
</tr>
<tr>
<td><strong>Haemoglobin A1c</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>per SD</td>
<td></td>
<td>1.23 (1.03-1.47)</td>
</tr>
<tr>
<td>Normal</td>
<td>24.8%</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>At risk for diabetes</td>
<td>45.5%</td>
<td>1.08 (0.66-1.76)</td>
</tr>
<tr>
<td>Elevated</td>
<td>29.7%</td>
<td>1.17 (0.70-1.97)</td>
</tr>
<tr>
<td><strong>Metabolic syndrome</strong></td>
<td>68.1%</td>
<td>0.82 (0.55-1.22)</td>
</tr>
</tbody>
</table>
The Next Steps

• 10/66 Third wave

• Dissemination! Dissemination! Dissemination!
Don’t forget

Sunday morning
10/66 Satellite Symposium
on Risk Factors
 Acknowledgments 10/66 Study

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  - Gilberto Perez, MD
  - Wendy Matos, PhD
  - Ivonne Z. Jiménez, MD - PI
“Your name may be forgotten, but don’t worry if your work is remembered”

Emil Kraepelin