Complex interventions to reduce blood pressure: focus on salt substitute trials

J. Jaime Miranda, MD, PhD

Lima, 26 March 2015
Conflict of interests

- **About me**
  - MD, PhD Epidemiología
  - CRONICAS Centro de Excelencia en Enfermedades Crónicas
  - IEA

- **Funding**
  - Wellcome Trust, NIH, IDRC, WHO, GCC

- No pharma funding
@jjaimemiranda

[Disclaimer]
Context matters
Latinoamérica

**In Focus**

International Poverty Centre

United Nations Development Programme

August 2005

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**Gávea**

**Rocinha**

**Poverty and the City**

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Value 1</th>
<th>Value 2</th>
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<tbody>
<tr>
<td>Human Development Index</td>
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<td>0.73</td>
</tr>
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<td>Life Expectancy at Birth</td>
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<td>67.3</td>
</tr>
<tr>
<td>Adult Literacy Rate</td>
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<td>87.9</td>
</tr>
<tr>
<td>Income Per Capita</td>
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<td>120.7</td>
</tr>
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<tr>
<td>Unemployment</td>
<td>12.4</td>
<td></td>
</tr>
</tbody>
</table>
“Burgeoning cities face catastrophe, says UN”

The new urban world

The world has become more urban than rural for the first time in human history. Some 4.5 billion people now live in urban areas, up from 2 billion 50 years ago. The map shows where people in cities live

Key
- Predominantly urban 75% or over
- Predominantly urban 50–74%
- Predominantly rural 25–49% urban
- Predominantly rural 0–24% urban
- Cities over 10 million people (greater urban areas)

US
246.2
Urban population in millions
81%
Urban percentage

Mexico
84.392
77%

Brazil
162.6
85%

China
559.2
Urban population in millions
42%
Urban percentage

India
329.3
29%

Indonesia
114.1
50%

The world’s urban population — from a total of 6.845.6 million

WEF – Global Risks Landscape 2009

- X axis: Likelihood
  - <1% to >20%

- Y axis: Severity (US$)
  - 2-10 billion to >1 trillion

- 6 Asset price collapse
- 31 Chronic disease
- 5 Fiscal crises
- 4 Slower China economy
- 33 Migration

Context hides opportunities
Differences in cardiovascular risk factors in rural, urban and rural-to-urban migrants in Peru

J Jaime Miranda,1,2,3 Robert H Gilman,1,4,5 Liam Smeeth1,3

ABSTRACT

Objectives To assess differences in cardiovascular risk profiles among rural-to-urban migrants and non-migrant groups.

Methods Cross-sectional study in Ayacucho and Lima, Peru. Participants were: rural (n=201); rural-to-urban migrants (n=589); and urban (n=199). Cardiovascular risk factors were assessed according to migrant status (migrants vs non-migrants), age at first migration, length of residency in an urban area and lifetime exposure to an urban area.

Results For most risk factors, the migrant group had intermediate levels of risk between those observed for the rural and urban groups. Prevalence for rural, migrant and urban groups was 3%, 20% and 33%, respectively, for obesity, and 0.8%, 3% and 6% for type-2 diabetes. This gradient of risk was not observed uniformly across all risk factors. Blood pressure did not show a clear gradient of difference between groups. The migrant group had similar systolic blood pressure but lower diastolic blood pressure areas within countries is less extensive. Because migration is often driven by economic and other factors that are likely to be related to health, migrants are often not representative of the rural area they come from, making valid comparisons between migrants and non-migrants difficult. During the period 1970 to the 1990s, mass migration from rural to urban areas occurred in Peru, triggered by political violence targeting rural dwellers.9 10 This meant that the usual selection effects that lead to migrants being an atypical group were reduced for two reasons. First, in affected areas, large proportions of the population migrated. Second, the key factor leading to migration was to escape from violence rather than economic forces. Particularly given the marked contrast between urban and rural lifestyles, Peru therefore offers a unique opportunity to assess the health effects of migration to urban areas. This
### Count of CVD risk factors

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<tr>
<td><strong>Migrant</strong></td>
<td>None</td>
<td>20</td>
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<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Rural</strong></td>
<td>None</td>
<td>20</td>
<td>4</td>
<td>2</td>
<td>1</td>
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<td></td>
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</table>
Major Cardiovascular Risk Factors in Latin America: A Comparison with the United States. The Latin American Consortium of Studies in Obesity (LASO)

J. Jaime Miranda¹,²,⁹, Victor M. Herrera³,⁴,⁹, Julio A. Chirinos⁵, Luis F. Gómez⁶, Pablo Perel⁷, Rafael Pichardo⁸, Angel González⁸, José R. Sánchez⁹, Catterina Ferreccio¹⁰, Ximena Aguilera¹¹, Eglé Silva¹², Myriam Oróstegui¹³, Josefina Medina-Lezama¹⁴, Cynthia M. Pérez¹⁵, Erick Suárez¹⁵, Ana P. Ortiz¹⁵, Luis Rosero¹⁶, Noberto Schapochnik¹⁷, Zulma Ortiz¹⁸, Daniel Ferrante¹⁹, Juan P. Casas²⁰, Leonelo E. Bautista³,⁹

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Abstract

Background: Limited knowledge on the prevalence and distribution of risk factors impairs the planning and implementation of cardiovascular prevention programs in the Latin American and Caribbean (LAC) region.

Methods and Findings: Prevalence of hypertension, diabetes mellitus, abnormal lipoprotein levels, obesity, and smoking were estimated from individual-level patient data pooled from population-based surveys (1998–2007, n = 31,009) from eight LAC countries and from a national survey of the United States (US) population (1999–2004). Age and gender specific prevalence were estimated and age-gender adjusted comparisons between both populations were conducted. Prevalence of diabetes mellitus, hypertension, and low high-density lipoprotein (HDL)-cholesterol in LAC were 5% (95% confidence interval: 3.4–7.9), 20.2% (95% CI: 12.5–31), and 53.3% (95% CI: 47–63.4), respectively. Compared to LAC region's
### Table 2. Age- and gender-adjusted prevalence ratios for major cardiovascular risk comparing each country against all the countries from Latin American and the Caribbean included in this study.

<table>
<thead>
<tr>
<th>Country</th>
<th>Hypertension</th>
<th>Diabetes</th>
<th>High total cholesterol</th>
<th>Smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>0.61*</td>
<td>1.12</td>
<td>0.84</td>
<td>0.41</td>
</tr>
<tr>
<td>Chile</td>
<td>1.48*</td>
<td>1.10</td>
<td>1.02</td>
<td>1.82*</td>
</tr>
<tr>
<td>Colombia</td>
<td>0.70</td>
<td>0.90</td>
<td>1.67*</td>
<td>0.65*</td>
</tr>
<tr>
<td>Costa Rica</td>
<td>1.15</td>
<td>1.40</td>
<td>1.86*</td>
<td>0.76*</td>
</tr>
<tr>
<td>Dominican Republic</td>
<td>1.31</td>
<td>1.25</td>
<td>0.83</td>
<td>0.74</td>
</tr>
<tr>
<td>Peru</td>
<td>0.65*</td>
<td>0.41*</td>
<td>0.75</td>
<td>0.68</td>
</tr>
<tr>
<td>Puerto Rico</td>
<td>1.19</td>
<td>2.89*</td>
<td>1.10</td>
<td>0.99</td>
</tr>
<tr>
<td>Venezuela</td>
<td>1.49</td>
<td>0.98</td>
<td>0.78</td>
<td>0.87</td>
</tr>
</tbody>
</table>
**Table 3.** Crude prevalence (%) of cardiovascular risk factors in the United States and the Latin American and the Caribbean populations, and age- and gender-adjusted prevalence ratios.

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Unites States*</th>
<th>Latin Americans</th>
<th>PR†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>95% CI</td>
<td>%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>30.5 (28.8; 32.2)</td>
<td>20.2 (12.5; 31.0)</td>
<td>0.93</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>8.2 (7.5; 8.8)</td>
<td>5.0 (3.4; 7.9)</td>
<td>0.86</td>
</tr>
<tr>
<td>High Total cholesterol</td>
<td>16.8 (15.8; 17.7)</td>
<td>8.9 (6.9; 11.4)</td>
<td>0.64</td>
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<tr>
<td>High LDL cholesterol</td>
<td>13.8 (12.6; 14.9)</td>
<td>8.5 (5.8; 12.2)</td>
<td>0.72</td>
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<td>Low HDL cholesterol</td>
<td>33.7 (32.2; 35.2)</td>
<td>53.3 (47.0; 63.4)</td>
<td>1.63</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>36.2 (34.4; 38.1)</td>
<td>26.5 (19.0; 35.7)</td>
<td>0.82</td>
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<tr>
<td>Smoking</td>
<td>21.0 (19.7; 22.4)</td>
<td>25.8 (18.1; 35.3)</td>
<td>1.13</td>
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<tr>
<td>Overall/Abdominal obesity</td>
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<td></td>
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<tr>
<td>BMI ≥30 kg/m²</td>
<td>31.0 (29.5; 32.5)</td>
<td>16.1 (11.1; 22.8)</td>
<td>0.58</td>
</tr>
<tr>
<td>WC ≥88/≥102 cm (women/men)</td>
<td>50.0 (48.2; 51.7)</td>
<td>35.8 (25.4; 47.8)</td>
<td>0.79</td>
</tr>
</tbody>
</table>
3
Addressing geographical variation in the progression of non-communicable diseases in Peru: the CRONICAS cohort study protocol

J Jaime Miranda,1,2 Antonio Bernabe-Ortiz,1,3 Liam Smeeth,1,4 Robert H Gilman,1,5,6 William Checkley,1,5,7 CRONICAS Cohort Study Group

ABSTRACT

Background: The rise in non-communicable diseases in developing countries has gained increased attention. Given that around 80% of deaths related to non-communicable diseases occur in low- and middle-income countries, there is a need for local knowledge to address such problems. Longitudinal studies can provide valuable information about disease burden of non-communicable diseases in Latin America to inform both public health and clinical settings.

Methods: The CRONICAS cohort is a longitudinal

ARTICLE SUMMARY

Article focus

- Compare prevalence and risk factors of cardiovascular and chronic obstructive pulmonary disease among three different populations.
- Compare rate of disease progression to hypertension and diabetes from a disease-free baseline status between populations.
- Compare rate of lung function decline between populations.

Site: Lima, urban “Pueblo Joven”
Site: rural Puno, near Bolivian border
Site: Tumbes, near Ecuadorian border
### Study settings

<table>
<thead>
<tr>
<th>Setting</th>
<th>Degree of urbanization</th>
<th>Use of biomass fuel</th>
<th>Outdoor air pollution</th>
<th>Altitude</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lima</td>
<td>Highly urbanized</td>
<td>Rare</td>
<td>High</td>
<td>Sea level</td>
</tr>
<tr>
<td>Tumbes</td>
<td>Semi-urban</td>
<td>Highly prevalent</td>
<td>Low</td>
<td>Sea level</td>
</tr>
<tr>
<td>Puno, urban</td>
<td>Urban</td>
<td>Rare</td>
<td>Low</td>
<td>3825 meters above sea level</td>
</tr>
<tr>
<td>Puno, rural</td>
<td>Rural</td>
<td>Highly prevalent</td>
<td>Low</td>
<td>3825 meters above sea level</td>
</tr>
</tbody>
</table>
CRONICAS Cohort study: Co-morbidities

- **Asthma**: 12% (Lima), 6.6% (Urban Puno), 31% (Rural Puno), 9.7% (Tumbes)
- **COPD**: 5.4% (Lima), 6.2% (Urban Puno), 10% (Rural Puno), 0% (Tumbes)
- **Diabetes**: 17.6% (Lima), 20.6% (Urban Puno), 19.9% (Rural Puno), 13.8% (Tumbes)
- **Depression**: 18.7% (Lima), 18.6% (Urban Puno), 0% (Rural Puno), 0% (Tumbes)
- **Alcoholism**: 0% (Lima), 0% (Urban Puno), 0% (Rural Puno), 0% (Tumbes)
- **Hypertension**: 17.7% (Lima), 11.3% (Urban Puno), 0% (Rural Puno), 0% (Tumbes)

Legend:
- 1% (Lightest color)
- 5% (Light color)
- 10% (Medium light color)
- 20% (Dark color)
Agreement Between Cardiovascular Disease Risk Scores in Resource-Limited Settings: Evidence from 5 Peruvian Sites

Juan Carlos Bazo-Alvarez,* Renato Quispe,* Frank Peralta,* Julio A. Poterico,*† Giancarlo A. Valle,* Melissa Burroughs,*‡§‖ Timesh Pillay,*|| Robert H. Gilman,*‡‖ William Checkley,*‡‡ Germán Malaga,*‡‡ Liam Smeeth,‖‖ Antonio Bernabé-Ortiz,* J. Jaime Miranda,*‡‡ and PERU MIGRANT Study; CRONICAS Cohort Study Group‖||

Abstract: It is unclear how well currently available risk scores predict cardiovascular disease (CVD) risk in low-income and middle-income countries. We aim to compare the American College of Cardiology/American Heart Association (ACC/AHA) Pooled Cohort risk equations (ACC/AHA model) with 6 other CVD risk tools to assess the concordance of predicted CVD risk in a random sample from 5 geographically diverse Peruvian populations. We used data from 2 Peruvian, age and sex-matched, population-based studies across 5 geographical sites. The ACC/AHA model were compared with 6 other CVD risk prediction tools: laboratory Framingham risk score for CVD, non-laboratory Framingham risk score for CVD, Reynolds risk score, systematic coronary risk evaluation, World Health Organization risk charts, and the Lancet chronic diseases risk charts. Main outcome was of choosing any of them for public health and clinical interventions in Latin American populations. There is a need to improve the evidence base of risk scores for CVD in low-income and middle-income countries.

Key Words: cardiovascular diseases, vulnerable populations, Peru

(source: Crit Pathw Cardiol 2015;XXX: 00–00)

Increasing rates of cardiovascular diseases (CVD) in low-income and middle-income countries (LMIC), and occurring at younger ages than seen in high-income countries, urge the need for action.\textsuperscript{1–3} Many public health interventions have arisen to prevent CVD in
CV risk in 10 years (Lin’s CCC)

- óptima concordancia teórica
- óptima concordancia empírica (FRS-B vs FRS-L)
- FRS-B vs RRS
- FRS-B vs ACC/AHA
- RRS vs ACC/AHA

CCC

FRS body mass continuous vs FRS lipids continuous

RRS vs ACC/AHA

FRS-B vs RRS

FRS-B vs ACC/AHA

RRS vs ACC/AHA

reynolds vs aip4

CCC

0

0.38

0.40

0.46

0.93

1
Relationship Between Daily Exposure to Biomass Fuel Smoke and Blood Pressure in High-Altitude Peru


Abstract—Household air pollution from biomass fuel use affects 3 billion people worldwide; however, few studies have examined the relationship between biomass fuel use and blood pressure. We sought to determine if daily biomass fuel use was associated with elevated blood pressure in high altitude Peru and if this relationship was affected by lung function. We analyzed baseline information from a population-based cohort study of adults aged ≥35 years in Puno, Peru. Daily biomass fuel use was self-reported. We used multivariable regression models to examine the relationship between daily exposure to biomass fuel smoke and blood pressure outcomes. Interactions with sex and quartiles of forced vital capacity were conducted to evaluate for effect modification. Data from 1004 individuals (mean age, 55.3 years; 51.7% women) were included. We found an association between biomass fuel use with both prehypertension (adjusted relative risk ratio, 5.0; 95% confidence interval, 2.6–9.9) and hypertension (adjusted relative risk ratio, 3.5; 95% confidence interval, 1.7–7.0). Biomass fuel users had a higher systolic blood pressure (7.01 mm Hg; 95% confidence interval, 4.4–9.6) and a higher diastolic blood pressure (5.9 mm Hg; 95% confidence interval, 4.2–7.6) when compared with nonusers. We did not find interaction effects between daily biomass fuel use and sex or percent predicted forced vital capacity for either systolic blood pressure or diastolic blood pressure. Biomass fuel use was associated with an increased risk of hypertension and higher blood pressure in Peru. Reducing exposure to household air pollution from biomass fuel use represents an opportunity for cardiovascular prevention. (Hypertension. 2015;65:00-00. DOI: 10.1161/HYPERTENSIONAHA.114.04840.)
Careful with “blaming the other”

Source: Vrijens et al. BMJ 2008;336:1114-1117
The other side

RESEARCH ARTICLE

Adherence to Pharmacotherapy and Medication-Related Beliefs in Patients with Hypertension in Lima, Peru

Marta Fernandez-Arias 1,2,9*, Ana Acuna-Villaorduna 1,3,9*, J. Jaime Miranda 1,4, Francisco Diez-Canseco 1, German Malaga 1,3,4,5

1. CRONICAS Centre of Excellence in Chronic Diseases, Universidad Peruana Cayetano Heredia, Lima, Peru, 2. Global Health, Brighton and Sussex Medical School, Brighton, United Kingdom, 3. Unidad de Conocimiento y Evidencia, Universidad Peruana Cayetano Heredia, Lima, Peru, 4. Facultad de Medicina “Alberto Hurtado”, Universidad Peruana Cayetano Heredia, Lima, Peru, 5. Servicio de Medicina Interna, Hospital Nacional Cayetano Heredia, Lima, Peru

*ana.acuna.vi@gmail.com

These authors contributed equally to this work.

These authors are joint first authors on this work.

What’s behind low-adherence?

- Beliefs of harm about medications and concerns about antihypertensive drugs higher in the low adherence group.

- Higher scores on ideas of harm were 52% less likely of being high adherents.

- Higher scores on concerns were 41% less likely of being high adherents.

- Patients whose ideas of necessity outweighed their concerns more likely to be adherent (PR 2.65; 95% CI 1.21–5.81).
So what?
Reflections #1

- Listen
- Opportunities
- Human factor is not constant!
- Specially for complex interventions
- Remove your vaccine-type of intervention
Now, Jaime, do your job.

- The title of the presentation was…?

- The project’s title is “Launching a salt substitute to reduce blood pressure at the population level in Peru”

- Protocol published, available in *Trials*
Effects of salt substitutes on blood pressure: a meta-analysis of randomized controlled trials

Ya-Guang Peng, Wei Li, Xiao-Xiao Wen, Ying Li, Ji-Hong Hu, and Lian-Cheng Zhao

Abstract

Background: Clinical trials assessing the effects of salt substitutes on blood pressure (BP) have reported mixed results.

Objectives: A meta-analysis of randomized controlled trials was conducted to evaluate the effect of salt substitutes on BP, including systolic BP (SBP) and diastolic BP (DBP).
Potassium supplementation for the management of primary hypertension in adults (Review)

Dickinson HO, Nicolson D, Campbell F, Beyer FR, Mason J
What we know

- Salt reduction beneficial, in general

- Salt substitutes (low-sodium salt)
  - SBP mean difference: $-4.9 \text{ mm Hg}; \text{ 95\% CI: } -7.3, -2.5$
  - DBP mean difference: $-1.5 \text{ mm Hg}; \text{ 95\% CI: } -2.7, -0.3$
  - Subjects with hypertension or high CVD risk
  - Not population based

- Potassium supplementation
  - Evidence is not conclusive.
Proposed site: Tumbes... context 😊
Study team

- Johns Hopkins University
  - Robert H. Gilman (PI)
  - Katherine A. Sacksteder (Co-investigator)

- Universidad Peruana Cayetano Heredia
  - J. Jaime Miranda (Co-PI)
  - Antonio Bernabe-Ortiz (Associate investigator)
  - Francisco Diez-Canseco (Associate investigator)
  - Maria Kathia Cardenas (Associate investigator)
Scope

- **Aim 1:** To assess patterns of predisposition towards incorporating a salt substitute into daily cooking among villagers, authorities, and other potential stakeholders in order to inform the structure of the intervention in the local communities and to ensure successful implementation.

**Phase 1: Exploratory Phase**

1.1. Triangle Taste Test (TTT)

1.2. Formative Research:

   Qualitative Study & Questionnaire to define Product Identity
Aim 2: To implement and assess the impact of an intervention using a salt substitute on blood pressure at the population level using a stepped wedge trial design.

Phase 2: Implementation Phase

1.1. Recruitment of participants & baseline
1.2. Production & distribution of salt substitute
1.3. Social Marketing Campaign

Aim 3: To determine the cost-effectiveness of this implementation strategy.
Where?

- **Setting:** Tumbes
- **Population:** ~200,000
- **Poverty level:** ~25.0%
- **Hypertension:** 26.9% (≥35 y/o, in 2010)
Setting

- 6 semi-rural villages
- Agriculture or fishing
- ~ 100-200 families or ~ 400-600 adults p/village
Exploratory Phase
Aim. Sensory discrimination test to assess if the use of potassium-enriched salt substitutes leads to perceived differences in taste.

Sample. 156 subjects (24 per village), 49% males, mean age 41 years (SD: 15.5)

Procedure. Samples of cooked rice were prepared with four different salts containing the following ratios of NaCl/KCl: 100/0 (regular table salt), 75/25, 66/33, and 50/50.