HOW TO MERGE AND COMPARE COHORT STUDIES
- CRIC & CKD-JAC -

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THE GOAL OF THIS PRESENTATION

• To illustrate approaches to harmonize data from cross-national cohort studies

• I will use the example of phosphate metabolism studies.
Challenges of Integrating Data across Cohorts

Variations in:

- Laboratory measurements
- Clinical phenotyping
- Outcome assessments
- Distributions of race/ethnicity
- Healthcare practice
CHALLENGES OF INTEGRATING DATA ACROSS COHORTS

Variations in:
• Laboratory measurements
• Clinical phenotyping
• Outcome assessments
• Distributions of race/ethnicity
• Healthcare practice
BACKGROUND: PHOSPHATE METABOLISM IN CKD

CKD

Renal failure
Dialysis

Vitamin D depletion
Secondary hyperparathyroidism
Hyperphosphatemia

Bone abnormality
Vascular calcification

Cardiovascular and all-cause death
BACKGROUND: PHOSPHATE METABOLISM IN CKD

• Combining Japanese and US data expands opportunities to study P\text{O}_4 metabolism.
• We hypothesized that P\text{O}_4 metabolism differs between Japan and the US.
• CKD-JAC and CRIC studies provide insights into US and Japanese CKD experience.
• Variations in CKD-JAC and CRIC’s laboratory measurements and clinical phenotyping must be addressed in an integrated analysis.
OVERARCHING AIM

• To evaluate how phosphate metabolism differ between Japanese and US CKD populations.
CKD-JAC AND CRIC

17 sites ~3000 pts
4-10 yrs (2007~JAC2)
eGFR 10-60 mL/min
(Elderly 10-50)

11 sites ~5500 pts
>10 yrs → CRIC phase IV
eGFR 20-70 mL/min
(Elderly 20-50)

Common outcomes:
CV events, deaths, eGFR, RRT, hospitalization, QOL
**Contrasts in Study Data: Laboratory Measures**

<table>
<thead>
<tr>
<th></th>
<th>CKD-JAC</th>
<th>CRIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Phosphate</td>
<td>Enzymatic assay (mg/dL)</td>
<td>Phosphomolybdate (mg/dL)</td>
</tr>
<tr>
<td>PTH</td>
<td>Intact PTH (pg/mL)</td>
<td>Total PTH (pg/mL)</td>
</tr>
<tr>
<td>FGF23</td>
<td>Intact FGF23 (pg/mL)</td>
<td>C-terminal FGF23 (RU/mL)</td>
</tr>
</tbody>
</table>
## Contrasts in Study Data: Clinical Measures

<table>
<thead>
<tr>
<th>Assessment of BMI</th>
<th>CKD-JAC</th>
<th>CRIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>WPRO criteria for Asians</td>
<td>WHO criteria for non-Asian participants</td>
</tr>
<tr>
<td>Category</td>
<td>BMI</td>
<td>Category</td>
</tr>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
<td>Underweight</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5 - &lt;23.0</td>
<td>Normal</td>
</tr>
<tr>
<td>Overweight</td>
<td>23.0 - &lt;25.0</td>
<td>Overweight</td>
</tr>
<tr>
<td>Obese I</td>
<td>25.0 - &lt;30.0</td>
<td>Obese I</td>
</tr>
<tr>
<td>Obese II</td>
<td>≥30.0</td>
<td>Obese II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Obese III</td>
</tr>
</tbody>
</table>

| Prior CVD         | Medical chart review | Self-report |
| Diet              | Diet History Questionnaire for Japanese | NCI Diet History Questionnaire |
| Medication        | Medical chart review | Self-report |
1. Combining data from two measurements of the same analyte (PO$_4$ and PTH)
   a. Create a “harmonization cohort”
      i. Internal – small sample of CKD-JAC or CRIC participants (e.g. PO$_4$)
Combining Data on 2 Measurements - Same Analyte Internal Approach: Serum PO4

<table>
<thead>
<tr>
<th></th>
<th>CRIC</th>
<th>CRIC internal</th>
<th>CKD-JAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>N of subjects with serum phosphate measurement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphomolybdate, mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enzymatic Assay, mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1. Combining data from two measurements of the same analyte ($PO_4$ and PTH)

a. Create a “harmonization cohort”
   i. Internal – small sample of CRIC or CKD-JAC participants ($PO_4$)
   ii. External – small set of CKD patients outside of CRIC or CKD-JAC (PTH)
**COMBINING DATA ON 2 MEASUREMENTS - SAME ANALYTE EXTERNAL APPROACH: PTH**

<table>
<thead>
<tr>
<th></th>
<th>CRIC</th>
<th>CKD-JAC</th>
<th>Hyogo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N of subjects with serum phosphate measurement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total PTH, pg/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact PTH, pg/mL</td>
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</table>
HOW TO HARMONIZE TWO MEASUREMENTS OF THE SAME ANALYTES

Deming Regression

A variation of linear regression that converts one measurement to another while incorporating measurement errors for both.
Generating Conversion Equations

Ordinary Least Square

Deming Regression

Measurements in CRIC

Measurements in CKD-JAC

Measurements in CRIC

Measurements in CKD-JAC
DEMING REGRESSION (PHOSPHATE)

Phosphate in CRIC

Phosphate in JAC

KDIGO
HARMONIZING PTH (EXTERNAL APPROACH)
1. Combining data from two measurements of the same analyte (PO$_4$ and PTH)
   a. Create a “harmonization cohort”
      i. Internal – small sample of CRIC or CKD-JAC participants
      ii. External – small set of CKD patients outside of CRIC or CKD-JAC

2. Combining data from related, but different analytes (FGF23)
   a. Repeat the assay for CRIC samples in CKD-JAC lab.
      i. “Full” set of CRIC samples sent to CKD-JAC lab.
### Combining 2 Different Analytes: FGF23

<table>
<thead>
<tr>
<th></th>
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<th>“Full” set of CRIC</th>
<th>CKD-JAC</th>
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<tbody>
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<td>N of subjects with serum phosphate measurement</td>
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<td>C-terminal FGF23, RU/mL</td>
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After Harmonization, the Difference Across Studies Increased: PO4
AFTER HARMONIZATION, THE DIFFERENCE ACROSS STUDIES APPEARED: PTH

<table>
<thead>
<tr>
<th>Observed</th>
<th>Harmonized</th>
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</table>

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**HARMONIZING CLINICAL PHENOTYPING: DIETARY PHOSPHATE**

<table>
<thead>
<tr>
<th>CRIC</th>
<th>CKD-JAC</th>
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<tbody>
<tr>
<td>NCI DHQ</td>
<td>Japanese DHQ</td>
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</table>

NCI DHQ and Japanese DHQ do not measure the same dietary constituents.

- We used urinary PO$_4$ excretion indexed to Ucr as a proxy for dietary intake available in both studies.
HARMONIZING CLINICAL PHENOTYPING: HISTORY OF CARDIOVASCULAR DISEASE

CRIC
Prior History based on self-report

CKD-JAC
Prior History based on medical chart

Goal: Convert “self-report” data to “medical chart” data in CRIC as collected in CKD-JAC
1. Studied 150 CRIC participants and collected medical chart-based data on CVD at the time of self-report
2. Used multiple imputation to create “medical chart” CVD data for all CRIC participants
DIFFERENCE ATTENUATED FOR CAD BUT NOT CHF

Observed

Harmonized
Difference between CRIC and CKD-JAC remained after data harmonization

- Challenges of data harmonization across cohorts can be addressed.
- Harmonization can lead to consequential changes in study findings.
- Residual difference requires additional investigation.
THANK YOU FOR YOUR ATTENTION