Determinants and Health Consequences of Gestational Diabetes Mellitus - A Life Course Perspective

Cuilin Zhang M.D., M.P.H., Ph.D.

Epidemiology Branch
Division of Intramural Population Health Research

Eunice Kennedy Shriver National Institute of Child Health and Human Development
Research Overview

Gestational Diabetes

- **Risk factors**
  - Diet & lifestyle
  - Genes

- **Pathogenesis**
  - Pathway specific
  - Systems biology

- **Health implications**
  - *beyond* pregnancy
    - Short & long-term
    - Women & children

**Type 2 diabetes**
- Diet & lifestyle
- Genes
- G*E interaction

**Obesity**
- Diet & lifestyle
- Genes
- Health consequences
**Gestational Diabetes Mellitus (GDM)**

*A growing health concern*

- Definition: glucose intolerance with onset/first recognition in pregnancy
- Common complication: 4~7% of pregnancies in U.S. (>240,000 cases /year)
- Prevalence is increasing: doubled (National Hospital Discharge Survey, 08)
- Related to adverse health outcomes (women + offspring)

<table>
<thead>
<tr>
<th>Women</th>
<th>Offspring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term</td>
<td>PIH, Preeclampsia</td>
</tr>
<tr>
<td>Beyond Pregnancy</td>
<td>Type 2 diabetes</td>
</tr>
</tbody>
</table>
**Risk of T2DM after GDM**

- Meta-analysis of the association
- 20 studies; 675,455 women; 10,859 T2DM events


<table>
<thead>
<tr>
<th>Country</th>
<th>T2DM/GDM</th>
<th>T2DM/no GDM</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>2874/21 823</td>
<td>6628/637 341</td>
<td>12.66 (12.15-13.19)</td>
</tr>
<tr>
<td>Korea</td>
<td>71/620</td>
<td>22/868</td>
<td>4.52 (2.83-7.21)</td>
</tr>
<tr>
<td>Hungary</td>
<td>21/68</td>
<td>0/39</td>
<td>24.93 (1.55-400.64)</td>
</tr>
<tr>
<td>USA</td>
<td>43/166</td>
<td>150/2242</td>
<td>3.87 (2.87-5.22)</td>
</tr>
<tr>
<td>France</td>
<td>53/295</td>
<td>1/111</td>
<td>19.94 (2.79-142.47)</td>
</tr>
<tr>
<td>Australia</td>
<td>405/5470</td>
<td>16/783</td>
<td>3.62 (2.21-5.93)</td>
</tr>
<tr>
<td>Brazil</td>
<td>6/70</td>
<td>7/108</td>
<td>1.32 (0.46-3.78)</td>
</tr>
<tr>
<td>India</td>
<td>13/35</td>
<td>8/489</td>
<td>22.70 (10.09-51.08)</td>
</tr>
<tr>
<td>Brazil</td>
<td>7/23</td>
<td>0/11</td>
<td>7.50 (0.47-120.11)</td>
</tr>
<tr>
<td>Finland</td>
<td>23/435</td>
<td>0/435</td>
<td>47.00 (2.86-771.65)</td>
</tr>
<tr>
<td>Spain</td>
<td>44/696</td>
<td>0/70</td>
<td>9.07 (0.56-146.25)</td>
</tr>
<tr>
<td>Sweden</td>
<td>21/229</td>
<td>1/61</td>
<td>5.59 (0.77-40.66)</td>
</tr>
<tr>
<td>Sweden</td>
<td>10/28</td>
<td>0/52</td>
<td>38.38 (2.33-631.74)</td>
</tr>
<tr>
<td>China</td>
<td>15/45</td>
<td>1/39</td>
<td>13.00 (1.80-93.93)</td>
</tr>
<tr>
<td>China</td>
<td>105/801</td>
<td>7/431</td>
<td>8.07 (3.79-17.19)</td>
</tr>
<tr>
<td>USA</td>
<td>10/15</td>
<td>0/35</td>
<td>47.25 (2.95-757.28)</td>
</tr>
<tr>
<td>Denmark</td>
<td>33/241</td>
<td>0/57</td>
<td>16.06 (1.00-258.06)</td>
</tr>
<tr>
<td>New Mexico</td>
<td>14/47</td>
<td>3/47</td>
<td>4.67 (1.43-15.21)</td>
</tr>
<tr>
<td>USA</td>
<td>224/615</td>
<td>18/328</td>
<td>6.64 (4.19-10.52)</td>
</tr>
<tr>
<td>Sweden</td>
<td>5/145</td>
<td>0/41</td>
<td>3.16 (0.18-55.76)</td>
</tr>
</tbody>
</table>

**Total**

<table>
<thead>
<tr>
<th>T2DM/GDM</th>
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<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3997/31867</td>
<td>6862/643588</td>
<td>7.43 (4.79-11.51)</td>
</tr>
</tbody>
</table>

Pooled RR = 7.43 (4.79, 11.51)
Risk of Hypertension after GDM

Gestational Diabetes Mellitus (GDM)  
A Growing Health Concern

- Common complication: 4~7% of pregnancies in U.S.
- Prevalence is increasing: Doubled
- Related to adverse health outcomes (women + offspring)

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<td>Beyond Pregnancy</td>
<td>Type 2 diabetes</td>
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<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The Vicious Circle: Diabetes Begets Diabetes

Type 2 diabetes (T2DM) → GDM → Impaired Adult Islet Function → Childhood Metabolic Disorders → ↑ Maternal Fuel to the Baby → Risk factors of GDM

Answering Research Questions

- Risk factors of GDM
- Pathogenesis of GDM: biomarkers
- Beyond pregnancy: determinants for the progression from GDM to adverse health outcomes
Modifiable Risk Factors of GDM

(8 years ago …)

- Overweight/obesity & cigarette smoking
- Very limited data on diet & exercise and GDM
- **Hypothesis:** diet & exercise are modifiable factors for GDM

- Metabolic and Animal studies: demonstrated above
- Non-pregnant individuals: diet & exercise can reduce T2DM risk

GDM ≠ ? T2DM

GDM has its own unique phenotypes

- Not all women with a history of GDM develop T2DM
- GDM is a pregnancy complication
  - Pregnancy concerns both women and fetus
  - During pregnancy, women experienced profound hormone, metabolic, and physiologic changes

Uncertain??

- Risk factors of T2DM are of GDM
- The magnitude and the effect size

We need data: diet, exercise → GDM ??
Diet, Lifestyle & GDM

GDM cohort in the Nurses’ Health Study II

- Population: women who reported at least 1 singleton pregnancy 1991-2005 (N=33,270)

- Primary analyses on physical activity and diet assessments used cumulative average information reported before GDM was diagnosed
What We Observed

- Physical activity
- Healthful patterns
  - Prudent pattern
  - Mediterranean diet
  - DASH
  - Healthy eating index
- Food
  - Nuts
  - Fruits
- Nutrient
  - Total fiber
  - Grain fiber
  - Fruit fiber
  - Vitamin D
  - Vegetable protein

- TV watching
- Western dietary pattern
- Food
  - Red meat
  - Processed meat
- Nutrient
  - Cholesterol
  - Saturated fat
  - Animal fat
  - Animal protein
  - Heme iron
  - Glycemic index
  - Glycemic load
- Sugar sweetened beverage

Zhang C  Am J Clin Nutr 2011
Physical Activity & GDM Risk
Why Physical Activity & GDM?

- **Mechanism Data**
  - Muscle contraction during PA $\uparrow$ muscle glucose uptake
  - Muscle glycogen synthesis is the major pathway for glucose metabolism, for promoting insulin sensitivity
  - $\downarrow$ fat + $\uparrow$ muscle mass ---- $\uparrow$ insulin sensitivity (long-term impact)

Sigal J et al Diabetes Care 2004
Zhang C et al Archives of Internal Medicine 2006
Physical Activity

A Prospective Study of Pregravid Physical Activity and Sedentary Behaviors in Relation to the Risk for Gestational Diabetes Mellitus

Summary of Major Findings

- Vigorous activity
- Walking pace (brisk)
- Flights of stair climbing
- TV watching

GDM risk

Zhang C et al Archives of Internal Medicine  2006
## Vigorous physical activity & GDM risk

<table>
<thead>
<tr>
<th>Vigorous Activity (Quintiles)</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range (MET-hrs/ wk)</td>
<td>0</td>
<td>0.2-2.8</td>
<td>2.9-8.7</td>
<td>8.8-22.0</td>
<td>≥22.1</td>
<td></td>
</tr>
<tr>
<td>No. Cases</td>
<td>397</td>
<td>262</td>
<td>270</td>
<td>275</td>
<td>224</td>
<td></td>
</tr>
</tbody>
</table>

| Adjusted RR *                | 1.00 | 0.95 | 0.84 | 0.75 | 0.77 | 0.002 |
|                             | (0.69, 0.94) |

* adjusted for age, race/ethnicity, cigarette smoking status, family history of diabetes, parity, alcohol intake, BMI, and total calories.
## Walking pace & GDM risk

<table>
<thead>
<tr>
<th>Usual walking pace</th>
<th>Casual</th>
<th>Normal</th>
<th>Brisk/ Very Brisk</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Cases</td>
<td>50</td>
<td>191</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>Adjusted RR*</td>
<td>1.00</td>
<td>0.81</td>
<td>0.66</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* adjusted for age, race/ethnicity, cigarette smoking status, family history of diabetes, parity, alcohol intake, BMI, physical activity and total calories
Pooled OR = 0.45 (0.28, 0.75)

Meta-analysis of Studies on Physical Activity & GDM (7 studies, 34,929 subjects)

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>OR (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chasan-Taber (2008)</td>
<td>0.80 (0.20, 2.70)</td>
<td>8.51</td>
</tr>
<tr>
<td>Harizopoulou (2009)</td>
<td>0.13 (0.06, 0.27)</td>
<td>13.9</td>
</tr>
<tr>
<td>Oken (2006)</td>
<td>0.70 (0.30, 1.68)</td>
<td>12.7</td>
</tr>
<tr>
<td>Redden (2010)</td>
<td>0.69 (0.46, 1.03)</td>
<td>18.0</td>
</tr>
<tr>
<td>Rudra (2006a)</td>
<td>0.14 (0.05, 0.38)</td>
<td>11.0</td>
</tr>
<tr>
<td>Rudra (2006b)</td>
<td>0.49 (0.28, 0.87)</td>
<td>16.1</td>
</tr>
<tr>
<td>Zhang (2006)</td>
<td>0.81 (0.68, 1.01)</td>
<td>19.8</td>
</tr>
<tr>
<td>Overall (I²=81.4%, p&lt;0.0001)</td>
<td>0.45 (0.28, 0.75)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

Tobias D et al Diabetes Care 2011
Diet, Lifestyle, & GDM

- **Physical activity**
- **Healthful dietary patterns**
  - Prudent pattern
  - Mediterranean diet
  - DASH
  - Healthy eating index
- **Foods**
  - Nuts
  - Fruits
- **Nutrients**
  - Total fiber
  - Grain fiber
  - Fruit fiber
  - Vitamin D
  - Vegetable protein

- **TV watching**
- **Western dietary pattern**
- **Foods**
  - Red meat
  - Processed meat
- **Nutrients**
  - Cholesterol
  - Saturated fat
  - Animal fat
  - Animal protein
  - Heme iron
  - Glycemic index
  - Glycemic load
- **Sugar sweetened beverage**

Zhang C Am J Clin Nutr 2011
A prospective study of dietary patterns, meat intake and the risk of gestational diabetes mellitus

- Two dietary patterns
  - Prudent - high in fruit, green leafy vegetables, poultry and fish
  - Western- high in red meat, processed meat, refined grains, sweets, and French fries

- Prudent pattern -- ↓ GDM risk
- Western pattern -- ↑ GDM risk

Zhang C et al Diabetologia 2007
## Dietary Patterns & GDM risk

<table>
<thead>
<tr>
<th>Quintiles</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Western dietary pattern</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.00</td>
<td>1.09</td>
<td>1.22</td>
<td>1.25</td>
<td>1.63</td>
<td>0.001</td>
</tr>
<tr>
<td>RR*</td>
<td>(1.20, 2.21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prudent dietary pattern</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.37</td>
<td>1.19</td>
<td>1.07</td>
<td>1.20</td>
<td>1.00</td>
<td>0.018</td>
</tr>
<tr>
<td>RR*</td>
<td>(1.09, 1.72)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* adjusted for age, race/ethnicity, cigarette smoking status, family history of diabetes, parity, alcohol intake, BMI, physical activity and the other dietary pattern

Zhang C et al Diabetologia 2007
# Red Meat, Processed Meat & GDM

<table>
<thead>
<tr>
<th></th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Red meat</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>≤0.21</td>
<td>0.28-0.35</td>
<td>0.42-0.56</td>
<td>0.57-0.85</td>
<td>≥0.86</td>
<td></td>
</tr>
<tr>
<td>RR*</td>
<td>1.00</td>
<td>1.25</td>
<td>1.52</td>
<td>1.73</td>
<td>1.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(1.35, 2.26)</td>
</tr>
<tr>
<td><strong>Processed meat</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0</td>
<td>0.07</td>
<td>0.14</td>
<td>0.21-0.35</td>
<td>≥0.42</td>
<td></td>
</tr>
<tr>
<td>RR*</td>
<td>1.00</td>
<td>1.29</td>
<td>1.33</td>
<td>1.58</td>
<td>1.68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(1.30, 2.16)</td>
</tr>
</tbody>
</table>

* adjusted for age, race/ethnicity, cigarette smoking status, family history of diabetes, parity, alcohol intake, BMI, physical activity and other dietary factors.
Potential Mechanisms

- Nitrites, preservatives in processed meat, were linked to β-cell toxicity

- Toxic effects of advanced glycation end products (AGEs), formed in meat and high fat products by heating
  - Diabetic mice: treatment with amino-guanidine, an AGE inhibitor
    - the progression of diabetes
    - the loss of β-cell secretory capacity

- Adverse effects of nutrient components in red meat on insulin sensitivity (saturated fat, cholesterol, protein, amino acids...)

Hofmann SM, *Diabetes* 2002
Prepregnancy Dietary Protein Intake, Major Dietary Protein Sources, and the Risk of Gestational Diabetes Mellitus

A prospective cohort study

↑ Animal protein  |  ↑ GDM risk

↑ Vegetable protein  |  ↓ GDM risk

Covariates adjusted in the multivariate model: age (5-year category) and parity (0, 1, 2, 3+), race/ethnicity, family history of diabetes (yes, no), cigarette smoking (never, past, current), alcohol intake (0, 0.1-5.0, 5.1-10.0 or >10 g/day), physical activity (quintile), and total energy intake (quintile), saturated fat (quintile), monounsaturated fat (quintile), polyunsaturated fat (quintile), trans fat (quintile), dietary cholesterol (quintile), glycemic load (quintile), dietary fiber (quintile), and mutual adjustment for animal protein and vegetable protein.

Relative risk for GDM

Quintiles of protein intake (median % energy/day)

P for trend 0.10

P for trend 0.01

P for trend 0.03
If no protein from red meat, then what should I eat to obtain protein?
Substitution of healthful protein sources for red meat at 1 serving/day

Diet, lifestyle factors & GDM

- Physical activity
- Healthful patterns
  - Prudent pattern
  - Mediterranean diet
  - DASH
  - Healthy eating index
- Food
  - Nuts
  - Fruits
- Nutrient
  - Total fiber
  - Grain fiber
  - Fruit fiber
  - Vitamin D
  - Vegetable protein
  - Cholesterol
  - Saturated fat
  - Animal fat
  - Animal protein
  - Heme iron
  - Glycemic index
  - Glycemic load

- TV watching
- Sugar sweetened beverage

Translate discovery into public health message
- Joint effects: modifiable factors & GDM risk

Zhang C Am J Clin Nutr 2011
Joint effects of modifiable factors

Four low risk modifiable factors

1. Moderate to vigorous exercise 30 minutes/day
2. Healthful dietary score in the upper two quintiles
3. Not-current smoking
4. BMI < 25 kg/m²
### Joint effects of modifiable factors

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>% Women</th>
<th>RR</th>
<th>PAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 factors in low-risk group (healthful diet, regular exercise, non-smoking)</td>
<td>14.9</td>
<td>0.58 (0.46, 0.73)</td>
<td>37 (24, 47)</td>
</tr>
<tr>
<td>4 factors in low-risk group (above + BMI&lt;25 kg/m²)</td>
<td>12.3</td>
<td>0.50 (0.35, 0.58)</td>
<td>46 (32-57)</td>
</tr>
</tbody>
</table>

Indicates 46% of the GDM cases might have been prevented if all women had been in the low-risk group for the four factors.
Joint effects of diet & lifestyle (exercise, healthful diet + non-smoking)

By body adiposity status: normal vs. overweight/obese

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>% Women</th>
<th>RR*</th>
<th>PAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 25</td>
<td>16.9</td>
<td>0.71 (0.54, 0.94)</td>
<td>25 (5, 40)</td>
</tr>
<tr>
<td>≥ 25</td>
<td>9.8</td>
<td>0.57 (0.38, 0.84)</td>
<td>40 (15, 58)</td>
</tr>
</tbody>
</table>

Among **overweight women**, 40% of the GDM cases might have been prevented if all women had been in the low-risk group of healthy diet and lifestyle.
Summary & Implications (Diet, Lifestyle & GDM)

- Diet and physical activity play an important role in the development of GDM - confirm our hypothesis

- A large proportion of GDM cases could be prevented by the adoption of a healthier diet and lifestyle

- It is not easy to change behavior/lifestyle. Pregnancy or family planning time may represent an ideal time to advocate for a healthy lifestyle for the family (pregnant women/women planning pregnancy are generally better motivated to follow advice to improve pregnancy outcomes)
Next Steps

- Identify risk factors
  - Other: sleep, environmental chemicals (endocrine disruptors: e.g. perfluorochemicals), etc.
- Translate findings into intervention, in high risk population
  - Improve metabolic phenotypes
  - Prevent GDM
  - Improve birth outcomes
- Investigate intermediate biomarkers and underlying molecular mechanisms; discover novel pathways and risk factors
Answering Research Questions

- Risk factors of GDM
- Pathogenesis of GDM: biomarkers
  - Beyond pregnancy: determinants for the progression from GDM to adverse health outcomes
Data Gaps

Pathogenesis
- Insulin resistance $\uparrow$ + relatively diminished insulin secretion
  - Precise molecular mechanisms: unclear

- Pregnancy: profound and intense metabolic & physiologic alterations (progressive insulin resistance, hyperlipidemia, etc.)

- Longitudinal biomarker data across pregnancy is critical for a comprehensive understanding of mechanisms: limited

Challenges - blood collection among pregnant women
- longitudinal
- early pregnancy
- fasting
- large sample size

Zhang C, et al. Hum Repro Update, under review
A Longitudinal Study of GDM Biomarkers
- the GDM component in the Fetal Growth Study

- Overarching Goal

Investigate biomarkers of GDM for a comprehensive understanding of the pathogenesis, early prediction of GDM, and discovery of novel pathways and metabolic underpinnings of GDM
Method

- Longitudinal blood collection (2,802 pregnant women, 4 race groups)
  - 1st, 2nd, 3rd trimester, 6 wks postpartum
  - As early as 10 wks of gestation
  - Fasting samples

- Include a high risk population of GDM
  - Obese pregnant women (N=468)

- In total: 107 GDM cases from 2,802 pregnant women
### Method

Longitudinal lifestyle, clinical, fetal growth data & bio-specimens

<table>
<thead>
<tr>
<th>Data Collection</th>
<th>Enrollment</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Delivery</th>
<th>Post-partum 6 weeks (GDM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening/Interview</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>2D &amp; 3D Ultrasound of Fetus</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Maternal Anthropometry</td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
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<td>Neonatal Anthropometry</td>
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<td>✓</td>
</tr>
<tr>
<td>Maternal Blood</td>
<td>✓</td>
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<td>✓</td>
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</tr>
<tr>
<td>Cord Blood &amp; Placenta</td>
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<tr>
<td>Diet &amp; Lifestyle</td>
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<td>Clinical Information</td>
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</table>
Method

- Selection of biomarker panels (pathway specific & systems biology)
  - Adipokines & related cytokines
  - Iron metabolism
  - Vitamin D metabolism
  - Mitochondrial function
  - Sex hormones
  - Placental hormones
  - Metabolomics
    - Targeted (i.e. amino acids, etc.)
    - Global/untargeted

Glucose Homeostasis

GDM
Specific Research Questions

Primary

- Are levels of selected biomarkers in the 1st and 2nd trimester before GDM diagnosis related to GDM?
- Is trajectory from 1st to 2nd trimester related to GDM?
- Does the association vary by body adiposity status and race/ethnicity?
Where We Are

Data collection has just been successfully completed (2008-2013)
  - Longitudinal biospecimens (compliance rate >90%)

Measurement of assays is underway

In the coming months, exploit the rich data resources to understand the pathogenesis and metabolic underpinnings of GDM and related birth outcomes.
  (e.g., comprehensive biomarker data + exquisitely detailed diet, lifestyle, clinical data, and u/s of fetal growth)

STAY TUNED!
Gestational Diabetes *Beyond* Pregnancy
GDM Beyond Pregnancy

- A history of GDM → 7 fold ↑ T2DM risk
- Cumulative incidence of T2DM: 18-60% in 20 yrs after GDM

*Lee AJ, et al Diabetes Care 2007*
GDM *Beyond Pregnancy*

- A history of GDM → 7 fold ↑ T2DM risk
- Cumulative incidence of T2DM: 18-60% in 20 yrs after GDM
- T2DM is a global epidemic: 10% U.S.
- Complications begun by the time of diagnosis
- The majority die from complications, 200 American lives/day

----→ Need to prevent or delay T2DM among GDM women

**Answering Research Questions**

- Risk factors of GDM
- Pathogenesis of GDM

- **Beyond pregnancy: determinants for the progression from GDM to T2DM and comorbidities**
Critical Data Gaps

- **Sparse data:** Determinants GDM→T2DM?

- **Challenge:** Lack of long-term study linking pregnancy to health outcomes in later life
  
  - Conventional approach: >10 yrs follow-up due to long latency of T2DM
  
  - Incidence of GDM and T2DM continues to rise!

  - **BE CREATIVE & ACT SOONER!**
Address Data Gaps- Our Approach

Hybrid design: retrospective cohort data + prospective data collection

- Built upon cohorts with detailed long-term follow-up data for women at reproductive age to identify and enroll a GDM cohort (N=≈4,000; NHSII + DNBC)

- Follow up the GDM cohort to collect new data and biospecimens

- Combine retrospective cohort data + new data being collected
  - Longitudinal data of > 25 years over women’s life span
Research Aims

- Identify and quantify determinants of the progression from GDM to T2DM and comorbidities
  - Genetic factors
  - Modifiable factors
  - Clinical factors
  - Gene*environment interactions

- Obtain baseline data on children from GDM pregnancies

Important for developing early & personalized prevention strategies
Data Collection

- Standardized questionnaires: diet, lifestyle, SES, medical history, etc.
- Bio-specimen collection
  - Fasting blood: serum, plasma, buffy coat, RBCs, DNA, RNA
  - First morning urine
  - Toenails

- Comparable and/or complementary approaches in NHSII & DNBC
  - DNBC- in-person clinical exam in Denmark
    - 2 hour OGTT test
    - Body fat distribution & bone mineral density (DEXA scan)
Welcome to the Diabetes & Women’s Health Study Website

What is GDM and who is affected?

Gestational diabetes mellitus (GDM), defined as glucose intolerance with onset or first recognition in pregnancy, currently affects 7-14% of pregnancies worldwide and its occurrence has been increasing in recent years.

Am I eligible to participate?

You are eligible to participate if you’ve had gestational diabetes in one or more pregnancies, 10 or more years ago.

Want to learn more?

Explore the links on this page to learn more about the Diabetes & Women’s Health Study. Find out what is involved for each participant, why we have reached out to you and more general health information about gestational diabetes and potential long-term health effects.
Where We Are
-- prospective data collection (www.dwhStudy.org)

✓ 3760 eligible participants were enrolled Nov. 2013

Diabetes & Women's Health Study: Enrollment Table

<table>
<thead>
<tr>
<th>Sites</th>
<th>Current Enrollment</th>
<th>Overall Targeted Enrollment</th>
<th>% of Overall Targeted</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNBC</td>
<td>745</td>
<td>1000</td>
<td>75</td>
</tr>
<tr>
<td>NHSII</td>
<td>3015</td>
<td>3000</td>
<td>100+</td>
</tr>
<tr>
<td>TOTAL</td>
<td>3760</td>
<td>4000</td>
<td>94</td>
</tr>
</tbody>
</table>
Where We Are
-- retrospective cohort data

☑ Data of the GDM cohort from the past >20 years in both NHSII and DNBC were assembled
# Healthful Dietary Patterns and Type 2 Diabetes Mellitus Risk Among Women With a History of Gestational Diabetes Mellitus

Deirdre K. Tobias, ScD; Frank B. Hu, MD, PhD; Jorge Chavarro, MD, ScD; Bernard Rosner, PhD; Dariush Mozaffarian, MD, DPH; Cui Lin Zhang, MD, PhD

<table>
<thead>
<tr>
<th>Dietary Patterns</th>
<th>Q1 (ref)</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>P value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>aMED</td>
<td>1.00</td>
<td>0.74</td>
<td>0.77</td>
<td>0.60 (0.44-0.82)</td>
<td>0.002</td>
</tr>
<tr>
<td>DASH</td>
<td>1.00</td>
<td>0.67</td>
<td>0.77</td>
<td>0.54 (0.39-0.73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>aHEI</td>
<td>1.00</td>
<td>0.72</td>
<td>0.60</td>
<td>0.43 (0.31-0.59)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- aMED: Alternate Mediterranean Diet
- DASH: Dietary Approaches to Stop Hypertension
- aHEI: Alternate Health Eating Index
Maternal Glucose Levels in Pregnancy and Offspring Long-term Growth in Childhood

- A prospective study of 665 women-offspring pairs from the historical data of DWH study- DNBC

- Weight and length/height at birth, 6 months, 1.5 yrs, and 7 yrs were used to calculate BMI Z-scores and percentiles

**Preliminary findings**

Each 10 mg/dl ↑ in maternal fasting glucose in pregnancy was significantly related to

- ↑ birthweight: 1.4 (0.5-1.9) unit
- ↑ BMI Z-score at 7 years: 0.09 (0.01-0.2) unit
- A 1.64-fold ↑ risk of obesity at 7 years
Next Steps

- Complete DWH study, addressing data gaps
  - Genetic and environmental determinants for the progression from GDM to T2DM and the molecular mechanisms
  - Confirm in other populations (e.g. non-Caucasians)

- Translate the findings into early prediction and prevention of T2DM and comorbidities

- Investigate the trans-generational impacts of hyperglycemia in pregnancy on offspring health (metabolic, cardio-vascular, reproduction, etc.) and underlying mechanisms
Interrupt the Vicious Circle

**Diabetes Begets Diabetes**

Answering Research Questions

- Risk factors of GDM
- Pathogenesis of GDM: biomarkers
- Beyond pregnancy: determinants for the progression from GDM to adverse health outcomes
Interrupt the Vicious Circle

Diabetes Begets Diabetes

- Impaired Adult Islet Function
- Childhood Metabolic Disorders
- ↑ Maternal Fuel to the Baby
- ↑ Maternal Islet Function
- T2DM

STOP DIABETES
• Training Opportunities

- NIH IRTAs (Intramural Research Training Award)
  - Pre-doctoral fellows
  - Post-doctoral fellows
  - Summer interns

zhangcu@mail.nih.gov
Division of Epidemiology, Statistics & Prevention Research (DESPR)

DESPR conducts research and supports research training in the fields of reproduction, child health, and maternal health as part of the NICHD's intramural research portfolio. The Division's research portfolio includes studies on infant mortality, biometry, mathematics, and statistical methodology and consultation; epidemiology; human fecundity and fertility; pregnancy complications and adverse pregnancy outcomes; childhood injuries; teen driving; pediatric infectious diseases; birth defects; and behavioral research in health promotion and disease prevention.

People

- Contact Info

Branches

- Biometry and Mathematical Statistics Branch
- DESPR Office of the Director
- Epidemiology Branch
- National Children's Study
- Prevention Research Branch
- Supported Networks, Programs, and Initiatives

Research Studies

- Biometry, Mathematics, and Statistics Studies
- Child Growth and Development Studies
- Child and Adolescent Behavior Studies
- Childhood Injury Studies
- Epidemiology of Bacterial Vaginosis
- Human Fecundity and Fertility Studies
- Management of Chronic Disease Studies
- NIH-DC Initiative to Reduce Infant Mortality in Minority Populations
- National Children's Study
- Pregnancy Studies
- Teen Driving Studies

http://www.nichd.nih.gov/about/org/diphcr
Thank You
Appendix 1
Conceptual Framework: Diabetes begets diabetes - genetic and non-genetic determinants for the progression from GDM-T2DM (maternal risk)

Genetic Factors
- TCF7L2
- HHEX
- CDKAL1
- IGFBP2
- SLC30A8
- CDKN2A/B
- KCNJ11
- PPARG
- Genetic Risk Score
- Others

Intermediate Biological Mechanism
- Dyslipidemia & Impaired Adipogenesis
  - Lipid profiles: triglyceride, HDL-C, LDL-C, LDL particle size, free fatty acids
- Adipokines: adiponectin, RBP4, leptin
- Systemic inflammation:
  - hs-CRP
  - IL-6
- Endogenous Sex-steroid hormone:
  - SHBG
  - Testosterone
- Endothelial dysfunction:
  - e-selectin
  - sICAM
  - sVCAM
- Others

Exogenous Modifiable Factors
- Obesity
- Excessive weight gain
- Smoking
- Physical activity
- Lactation
- Sleep duration
- Dietary factors:
  - Prudent diet pattern
  - Dietary fiber
  - Polyunsaturated FA

Other Factors
- Fetus factors: gender, parity, birth order
- Reproductive history
  - Age of menarche, menstrual cycle, etc.
- Medical history
- Early life factors
  - Birth weight, premature birth
- Others

GDM

Glucose intolerance in pregnancy

Time Line
chronic metabolic & vascular disorders in later adulthood

Chronic Metabolic & Vascular Disorders
- Type 2 DM
- Vascular disorders

??
- It was observed that maternal diabetes induces
  - fetal hyper-glycaemia
  - islet cell hypertrophy
  - beta cell hyperactivity
  → fetal hyper-insulinaemia and excess growth

- Emerging findings suggested that impact of hyperglycemia on offspring growth is continuum

- Epi studies on the long-term health impact of intrauterine exposure to hyperglycemia on childhood growth are relatively limited and findings are inconsistent.
Maternal glucose in pregnancy & offspring BMI Z-score change from birth to childhood

- Linear mixed-effect model

<table>
<thead>
<tr>
<th>Variables</th>
<th>Estimate</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal glucose</td>
<td>-0.1898</td>
<td>0.0483</td>
</tr>
<tr>
<td>Maternal age</td>
<td>-0.00340</td>
<td>0.7521</td>
</tr>
<tr>
<td>Offspring age</td>
<td>-0.0579</td>
<td>0.0891</td>
</tr>
<tr>
<td>Offspring gender</td>
<td>-3.2340</td>
<td>0.2063</td>
</tr>
<tr>
<td>Maternal pre-pregnancy BMI</td>
<td>0.0788</td>
<td>0.3062</td>
</tr>
<tr>
<td>Maternal glucose* offspring age</td>
<td>0.0143</td>
<td>0.0635</td>
</tr>
<tr>
<td>Maternal glucose * offspring gender</td>
<td>0.7136</td>
<td>0.2175</td>
</tr>
<tr>
<td>Maternal glucose * offspring birth Z score</td>
<td>-0.6972</td>
<td>0.0251</td>
</tr>
<tr>
<td>Maternal glucose * pre-pregnancy BMI</td>
<td>-0.0109</td>
<td>0.5244</td>
</tr>
</tbody>
</table>
Flow Diagram of Study Population

Initially identified GDM cases (NHSII)  
N=6,500

Initially identified GDM cases (DNBC)  
N=1,400

Exclude:  
• T2D w/in 1 year  
• Diabetes before pregnancy  
• Death

NHS-II Eligible Participants  
N=5,987

DNBC Eligible Participants  
N=1,250

Exclude:  
• Non-response  
• Unwilling to provide informed consent

Final Participants with biospecimen collection  
(N=~4,000)  
NHSII (N=~3,000); DNBC (N=~1,000)
Study Methods
(Prospective data collection)

- Standardized questionnaires at baseline & 2 years after
  - Diet
  - Physical activity and other lifestyle factors (e.g. sleep)
  - Demographic & SES
  - Psycho-social factors
  - Reproductive characteristics
  - Medical history
  - Family history
  - Anthropometry
  - Others
  - Characteristics and health status of **offspring**
    - SES
    - Reproductive: menarche, menstrual cycle, puberty, etc.
    - Life course weight characteristics
    - Medical history: metabolic and vascular, PCOS, etc.
Ascertainment of T2DM

T2DM diagnosis is established if one or more of the following criteria are met:

1. an elevated glucose concentration (fasting plasma glucose level ≥ 7.8 mmol/L (140 mg/dL), random plasma glucose level ≥ 11.1 mmol/L (200 mg/dL), or plasma glucose level ≥ 11.1 mmol/L (200 mg/dL) after an oral glucose load) and at least one symptom related to diabetes (excessive thirst, polyuria, weight loss, or hunger);

2. no symptoms but elevated glucose concentrations on two occasions; and

3. treatment with insulin or oral hypoglycemic medication.
Healthful Diet

- Alternate Mediterranean Diet (aMED)
- Dietary Approaches to Stop Hypertension (DASH)
- Alternate Health Eating Index (aHEI)
<table>
<thead>
<tr>
<th>Group</th>
<th>% Women</th>
<th>No. of GDM Events</th>
<th>Relative Risk†</th>
<th>95% CI</th>
<th>PAR %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current non-smoker</td>
<td>91.9%</td>
<td>730</td>
<td>0.77</td>
<td>0.63, 0.94</td>
<td>2.7%</td>
<td>0.7, 4.3</td>
</tr>
<tr>
<td>BMI&lt;25 kg/m²</td>
<td>72.7%</td>
<td>412</td>
<td>0.42</td>
<td>0.37, 0.48</td>
<td>29.1%</td>
<td>26.1, 31.6</td>
</tr>
<tr>
<td>aHEI-2010 diet score in upper 2 quintiles</td>
<td>39.3%</td>
<td>261</td>
<td>0.73</td>
<td>0.63, 0.85</td>
<td>18.5%</td>
<td>10.3, 25.3</td>
</tr>
<tr>
<td>Moderate/vigorous exercise ≥150 minutes/week</td>
<td>28.4%</td>
<td>177</td>
<td>0.83</td>
<td>0.70, 0.99</td>
<td>13.4%</td>
<td>0.8, 23.6</td>
</tr>
</tbody>
</table>

† Relative risk was adjusted for age, other variables included in the table, parity, family history of diabetes, history of infertility, race/ethnicity, questionnaire period, total energy intake
Potential Mechanisms

- **Potential mechanisms**
  - Different amino acids components: animal vs. vegetable protein
  - Branched-chain amino acid (BCAA): significantly ↑ after an animal protein-rich meal
  - Circulating BCAA levels were related to gluconeogenesis and insulin resistance (Cell Metab 2009) (Nat Med 2010)
Branched Amino Acids & GDM

Excessive dietary intake (e.g., high animal protein)

↑ Glutamate

↑ BCAAs

mTOR

↑ S6K1

↑ IRS-1

↑ Alanine

Pyruvate

BCKAs

α-KG

↑ Glutamate

↑ Alanine

↑ Adipogenesis

↓ Glucose transport

Insulin resistance

↑ Gluconeogenesis

↑ GDM

Genes

mTOR

Lipin

PPARγ

↑ Adipogenesis

↓ Glucose transport

Insulin resistance

↑ Gluconeogenesis

↑ GDM

Nat Med 2010
Iron metabolism and GDM

↑ Dietary & supplemental Iron intake
(Heme & Non-heme Iron)

Other factors

↑ Body iron stores
(e.g., Ferritin, Hepcidin, HO-1)

Inflammation

Mitochondrial dysfunction

Oxidative stress

Endoplasmic reticulum stress

β-cell dysfunction
↑ - β- cell apoptosis
↓ Insulin secretion

Insulin resistance
↑ FFA oxidation
↑ Hepatic glucose output
↓ Peripheral glucose uptake

Pregnancy

GDM
### Dietary Iron Intakes and GDM

**Bowers K, Zhang C et al.. Diabetes Care 2011 (with discussion)**

<table>
<thead>
<tr>
<th>Heme iron intake</th>
<th>Median (mg/day)</th>
<th>Fully Adjusted</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 (ref)</td>
<td>0.66</td>
<td>1.00 (ref)</td>
<td>n/a</td>
</tr>
<tr>
<td>Q2</td>
<td>0.90</td>
<td>1.13 (0.88, 1.45)</td>
<td>0.33</td>
</tr>
<tr>
<td>Q3</td>
<td>1.10</td>
<td>1.35 (1.05, 1.72)</td>
<td>0.02</td>
</tr>
<tr>
<td>Q4</td>
<td>1.30</td>
<td>1.57 (1.23, 2.02)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Q5</td>
<td>1.60</td>
<td>1.70 (1.30, 2.23)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Trend</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**NHSII data**

**NHSII:** *Bowers K, Zhang C et al.. Diabetes Care 2011*

**Omega study:** *Qiu C, Zhang C et al. Diabetes Care 2011*

**Danish National Birth Cohort:** *Zhang C, et al. SER, 2012. in preparation*

**Heme-iron supplement, iron metabolism biomarkers, & GDM:** *NIH ODS funding, 2012-13*
Metabolic risk factors

Age

Pregnancies

The normal physiological response to pregnancy represents a transient excursion into metabolic disorders

- Hyperlipidemia
- Insulin resistance

Fetus, placenta

Hormonal change

Carbohydrate & Lipid pathways

stress test
- Pregnancy related metabolic challenges **UNMASK** a predisposition to glucose metabolic disorders
- Factors affect glucose homeostasis before pregnancy can have adverse effects during pregnancy and be risk factors for GDM
Dietary & lifestyle factors during pregnancy were not measured

- Biological plausible:
  - Pre-pregnancy diet & lifestyle affect the underlying susceptibility to glucose intolerance when facing metabolic challenges in pregnancy

  - The normal physiological response to pregnancy represents a **transient excursion** into metabolic disorders

  - Metabolic responses to pregnancy could be considered as “**STRESS**” tests

  - Pregnancy related metabolic challenges **UNMASK** a predisposition to glucose metabolic disorders

  - Factors affect insulin sensitivity / secretion (before pregnancy) can have a deleterious effect during pregnancy and be risk factors for GDM
### Major Findings on Adipokines and GDM (by August, 2013)

<table>
<thead>
<tr>
<th>Adipokines</th>
<th>Number of Studies and Major Findings</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Prospective study</td>
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<tr>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>RBP-4</td>
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<tr>
<td>Resistin</td>
<td>2</td>
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<tr>
<td>TNF-alpha</td>
<td>3</td>
</tr>
<tr>
<td>IL-6</td>
<td>2</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>9</td>
</tr>
<tr>
<td>Leptin</td>
<td>6</td>
</tr>
<tr>
<td>Visfatin</td>
<td>1</td>
</tr>
</tbody>
</table>

↑ positive association, ↓ inverse association, ↔ non-significant difference (p>0.05)
### Appendix 1

**Table 1. Selected biomarkers for the study of the pathogenesis of gestational diabetes**

<table>
<thead>
<tr>
<th>Name (Symbol)</th>
<th>Method (Company, Instrument)</th>
<th>Material</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Adipokines and related cytokines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adiponectin, total</td>
<td>ELISA (Millipore)</td>
<td>Serum/EDTA plasma</td>
</tr>
<tr>
<td>Adiponectin, high molecular weight</td>
<td>ELISA (Millipore)</td>
<td>Serum/EDTA plasma</td>
</tr>
<tr>
<td>C-reactive Protein, High Sensitive (hsCRP)</td>
<td>Immunoturbidimetric assay (Roche Diagnostics, Roche/Hitachi Modular P Chemistry analyzer)</td>
<td>Serum/EDTA plasma</td>
</tr>
<tr>
<td>Fatty acid binding protein 4 (FABP4)</td>
<td>ELISA (BioVendor)</td>
<td>Serum/EDTA plasma</td>
</tr>
<tr>
<td>Interleukin-6 (IL-6)</td>
<td>ELISA (R&amp;D)</td>
<td>Serum/EDTA plasma</td>
</tr>
<tr>
<td>Leptin</td>
<td>RIA (Millipore)</td>
<td>Serum/EDTA plasma</td>
</tr>
<tr>
<td>Leptin Receptor, soluble</td>
<td>ELISA (R&amp;D)</td>
<td>Serum/EDTA plasma</td>
</tr>
<tr>
<td>Omentin-1</td>
<td>ELISA (R&amp;D)</td>
<td>Serum/EDTA plasma</td>
</tr>
<tr>
<td>Retinol Binding Protein-4 (RBP-4)</td>
<td>ELISA (ALPCO Diagnostics)</td>
<td>Serum/EDTA plasma</td>
</tr>
<tr>
<td>Vaspin</td>
<td>ELISA (AdipoGen)</td>
<td>Serum/EDTA plasma</td>
</tr>
<tr>
<td><strong>2. Metabolic Markers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>Chemiluminescent immunoassay (Roche Diagnostics, Roche Elecsys 2010 Analyzer)</td>
<td>Serum/EDTA plasma</td>
</tr>
<tr>
<td>Insulin-like growth factor 1 (IGF-1)</td>
<td>ELISA (Diagnostic Systems Laboratory)</td>
<td>Serum/EDTA plasma</td>
</tr>
<tr>
<td>Insulin-like growth factor binding protein 2 (IGFBP2)</td>
<td>ELISA (BioVendor)</td>
<td>Serum/EDTA plasma</td>
</tr>
<tr>
<td>Name (Symbol)</td>
<td>Method (Company, Instrument)</td>
<td>Material</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-----------------------------------------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>25-OH Vitamin D3</td>
<td>Quattro Tandem Mass Spectrometer</td>
<td>Serum</td>
</tr>
<tr>
<td></td>
<td>LC/MS (Waters 2795 Liquid Chromatogram &amp; Micromass ResHPLC)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quattro Tandem Mass Spectrometer</td>
<td></td>
</tr>
<tr>
<td>Sex Hormone Binding Globulin (SHBG)</td>
<td>Chemiluminescent immunoassay (Roche Diagnostics, Roche Elecsys 2010 Analyzer)</td>
<td>Serum</td>
</tr>
<tr>
<td>Estradiol</td>
<td>Chemiluminescent immunoassay (Roche Diagnostics, Roche Elecsys 2010 Analyzer)</td>
<td>Serum/EDTA plasma</td>
</tr>
<tr>
<td>Progesterone</td>
<td>Chemiluminescent immunoassay (Roche Diagnostics, Roche Elecsys 2010 Analyzer)</td>
<td>Serum/EDTA plasma</td>
</tr>
<tr>
<td></td>
<td>LC/MS (Waters Acquity Liquid Chromatogram &amp; Micromass ResHPLC)</td>
<td></td>
</tr>
<tr>
<td>Testosterone</td>
<td>Quattro Tandem Mass Spectrometer</td>
<td>Serum/EDTA plasma</td>
</tr>
<tr>
<td>5. Metabolomics markers</td>
<td>ESQ-MS/MS</td>
<td>EDTA plasma</td>
</tr>
<tr>
<td>Acylcarnitines</td>
<td>Amino Acid analyzer (Hitachi L-8900)</td>
<td>EDTA plasma</td>
</tr>
<tr>
<td>Amino acids</td>
<td>Varian CP7420 100m Column &amp; Hewlett Packard 5890 Gas Chromatograph</td>
<td>EDTA plasma</td>
</tr>
<tr>
<td>Fatty Acids</td>
<td>Agilent 1200 LC/6530 QTOF</td>
<td>EDTA plasma</td>
</tr>
<tr>
<td>Non-targeted Metabolomics</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Preliminary findings
Metabolomics & GDM

Permutation test: $p = 0.0218$

*Gas chromatography time-of-flight mass spectrometry*

Permutation test: $p = 0.0442$
Metabolomics & GDM

• Metabolomics, the global sets of low molecular weight metabolites in the body, provides a ‘snapshot’ of the metabolic status in the body in relation to genetic variations or external exposures.

• **Longitudinal** metabolomics data across pregnancy

Metabolic Phenotypes
- Obesity
- Insulin resistance
- T2DM

GDM
Diabetes: an Epidemic of 21st Century

- 10% of Americans (21 million) - currently
- 1/3 Americans - by 2050
- Complications have begun by the time of diagnosis
- Majority die of complications
- Important to identify high-risk population
  & develop early prevention strategies

Outline

- Introduction/background
- Risk factors of gestation diabetes (GDM)
- Pathogenesis & biomarkers of GDM
- GDM beyond pregnancy
  - Diabetes & Women’s Health Study
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