Prevention of diabetes and its complications

George L. King, MD
Joslin Diabetes Center
Harvard Medical School
Adjusted Prevalence of Diabetes and IFG, by BMI and Race*(NY Study)

- Normal Weight
  - Non-Hisp White: 20%
  - Non-Hisp Black: 22%
  - Non-Hisp Asian: 24%
  - Hispanic: 27%

- Overweight
  - Non-Hisp White: 42%
  - Non-Hisp Black: 57%
  - Non-Hisp Asian: 36%

- Obese
  - Non-Hisp White: 58%
  - Non-Hisp Black: 60%
  - Non-Hisp Asian: 45%

- BMI Category

- Non-Hisp White
- Non-Hisp Black
- Non-Hisp Asian
- Hispanic

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\*Models adjusted for sex, age, place of birth, income and physical activity

Thorpe et al, Diabetes Care 2009

- Estimate is higher than all other racial/ethnic groups at p<0.05
- Estimate is higher than whites at p<0.05
- Estimate is higher than whites (p<0.001) and Hispanics (p<0.05)
- Estimate is higher than blacks at p<0.05
# Two Main Types of Diabetes

<table>
<thead>
<tr>
<th>Type 1 diabetes</th>
<th>Type 2 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-10% of total</td>
<td>&gt;95% of total in AA</td>
</tr>
<tr>
<td>(rare in AA)</td>
<td>Mostly in adults, but increasing in children</td>
</tr>
<tr>
<td>Common in children</td>
<td>Not insulin requiring</td>
</tr>
<tr>
<td>Insulin Requiring</td>
<td>Insulin resistant</td>
</tr>
<tr>
<td>Auto-immune</td>
<td>Related to weight</td>
</tr>
<tr>
<td>Destruction of the Islets (minority in AA)</td>
<td></td>
</tr>
</tbody>
</table>
Insulin Sensitive

**Contributing Factors**
- Obesity
- Diet
- Sedentary Lifestyle
- Increasing Age
- Genetics
- Perinatal Factors

Insulin Resistant
Compensatory Hyperinsulinemia

**β Cell Decompensation**
- Relative Insulin Deficiency

**Normoglycemia**
- AMPK
- IKK
- IR Kinase
- DGAP

**Impaired Glucose Tolerance or ‘Prediabetes’**

**Type 2 Diabetes**
- β Cell Failure

**Risk of Cardio-vascular Complications**
- PKC
- MAPK
- AMPK
- Carbonic anhydrase

**Natural History of Type 2 Diabetes**

**Human Array**
Proposed BMI standards for overweight and obesity in Asians (compared to Whites)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Asian</th>
<th>White</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
<td>&lt;18.5</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5-22.9</td>
<td>18.5-24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>≥23</td>
<td>≥25</td>
</tr>
<tr>
<td>Pre-obese</td>
<td>23-24.9</td>
<td>25-29.9</td>
</tr>
<tr>
<td>Obese I</td>
<td>25-29.9</td>
<td>30-34.9</td>
</tr>
<tr>
<td>Obese II</td>
<td>≥30</td>
<td>35-39.9</td>
</tr>
<tr>
<td>Obese III</td>
<td></td>
<td>≥40</td>
</tr>
</tbody>
</table>

WHO Task Force: The Asia-Pacific Perspective: Redefining Obesity and Its Treatment. 2000
# Odds Ratio of Type 2 DM By Race and Ethnicity

<table>
<thead>
<tr>
<th></th>
<th>White</th>
<th>Asian</th>
<th>Pacific Is</th>
<th>Hispanic</th>
<th>Black</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>26.8 ± 0.2</td>
<td>24 ± 0.2</td>
<td>27.8 ± 0.5</td>
<td>27.9 ± 0.1</td>
<td>28.7 ± 0.1</td>
</tr>
<tr>
<td>1.0</td>
<td>1.0(0.7-1.4)</td>
<td>3.1(1.4-6.8)</td>
<td>2.0(1.8-2.3)</td>
<td>2.3(2.1-2.6)</td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td>1.6(1.1-2.2)</td>
<td>3.0(1.4-6.7)</td>
<td>1.9(1.6-2.1)</td>
<td>1.9(1.7-2.2)</td>
<td></td>
</tr>
<tr>
<td>1.0</td>
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<td>3.0(1.4-6.7)</td>
<td>1.9(1.6-2.1)</td>
<td>1.9(1.7-2.1)</td>
<td></td>
</tr>
</tbody>
</table>

Model 1, adjusted for age and sex
Model 2, adjusted for age, sex and BMI
Model 3, adjusted for age, sex, BMI, and health insurance status

McNeely: Diabetes Care 2004; 27(1) 66-69
The Diabetes Prevention Program

Sponsored by the NIH, NIDDK, NIA, NICHD, IHS, CDC, ADA and other agencies and corporations
Diabetes incidence rates by age

Lifestyle Metformin Placebo

25-44 (n=1000) 45-59 (n=1586) > 60 (n=648)
Percent developing diabetes by race-ethnicity

![Bar chart showing the percent developing diabetes by race-ethnicity.](chart)

- Caucasian (n=1768)
- African American (n=645)
- Hispanic (n=508)
- American Indian (n=171)
- Asian (n=142)
The Eight Strategies
For Avoiding, Controlling, or Reversing Diabetes
Strategy 1: The Rural Asian Diet (RAD)
Eating Plan: Cut Your Fat Intake in Half and Double Your Fiber
Nutrients Distribution in a Traditional Rural Asian Diet and Typical Western Diet

**Tradition Asian Diet**
- 40-45 kcal/kg
- 70% Carbohydrates
- 15% protein
  - 20% animal protein
- 15% Fat

**Typical Western Diet**
- 33 kcal/kg
- 50% Carbohydrates
- 16% protein
  - 60-80% animal protein
- 34% Fat
Available at: www.aadi.joslin.org

Recipes

AADI Recipe
– Shrimp Fried Rice

White rice is typically used in making fried rice. This recipe uses a healthier alternative, brown rice, which gives more nutrients and more fiber.

Ingredients:
- 2 tablespoons oyster sauce
- 1 tablespoon low sodium soy sauce
- 1 tablespoon canola oil
- 1 large egg, lightly beaten
- 3 cups cooked brown rice
- 2/3 cup frozen peas and carrots, defrosted
- 1/2 pound shrimp, precooked
- 2 tablespoons scallions, minced

Directions:
1. In a small bowl, mix the oyster sauce and soy sauce together. Set aside.
2. In a large frying pan or wok over high heat, heat the oil. Add the egg, and scramble with a spatula or wooden spoon.
3. Lower the heat to medium and add the rice, peas and carrots, stirring to break up any grains of rice that stick together.
4. After a few minutes, when the rice and vegetables are hot, add the shrimp, and then drizzle in the oyster-soy sauce mixture.
5. Add the scallions, stir to distribute the ingredients. Serve immediately.

Servings: 4
## Asian 10 day Menus
(Several meals are subject to change)

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breakfast</strong></td>
<td><strong>Breakfast</strong></td>
<td><strong>Breakfast</strong></td>
<td><strong>Breakfast</strong></td>
<td><strong>Breakfast</strong></td>
</tr>
<tr>
<td>Miso Soup</td>
<td>Seaweed</td>
<td>Soy Milk</td>
<td>Tofu Udon Soup</td>
<td>Seaweed</td>
</tr>
<tr>
<td>Brown Rice</td>
<td>Teriyaki Chicken</td>
<td>High fiber Cereals</td>
<td>Teriyaki Chicken</td>
<td>Brown Rice</td>
</tr>
<tr>
<td>Apple</td>
<td>Brown Rice</td>
<td>Yogurt</td>
<td>Brown Rice</td>
<td>Snap Peas</td>
</tr>
<tr>
<td>Vegetable Juice</td>
<td>Vegetable Juice</td>
<td>Grapes</td>
<td>Asparagus</td>
<td>Carrot Juice</td>
</tr>
<tr>
<td></td>
<td>Grapes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lunch</strong></td>
<td><strong>Lunch</strong></td>
<td><strong>Lunch</strong></td>
<td><strong>Lunch</strong></td>
<td><strong>Lunch</strong></td>
</tr>
<tr>
<td>Hoisin Pork</td>
<td>Pork Lo Mein</td>
<td>Garlic Tofu &amp; Bell Peppers</td>
<td>Sesame Peanut</td>
<td>Garlic Chicken</td>
</tr>
<tr>
<td>Chinese Broccoli</td>
<td>Brown Rice</td>
<td>Brown Rice</td>
<td>Chicken with Asparagus</td>
<td>Brown Rice</td>
</tr>
<tr>
<td>Sweet Potatoes</td>
<td>Tangerines</td>
<td>Tangerines</td>
<td>Brown Rice</td>
<td>Snap Peas</td>
</tr>
<tr>
<td>Grapes</td>
<td>Tangerines</td>
<td>Tangerines</td>
<td>Tangerines</td>
<td>Carrot Juice</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Dinner/Snack</strong></td>
<td><strong>Dinner/Snack</strong></td>
<td><strong>Dinner/Snack</strong></td>
<td><strong>Dinner/Snack</strong></td>
<td><strong>Dinner/Snack</strong></td>
</tr>
<tr>
<td>Chicken</td>
<td>Fried Rice</td>
<td>Chicken Soba Soup</td>
<td>Shrimp Teriyaki</td>
<td>Curry Shrimp</td>
</tr>
<tr>
<td>Soba Noodles</td>
<td></td>
<td>Soba Noodles</td>
<td>Soy Sauce</td>
<td>Stir fried Noodles</td>
</tr>
<tr>
<td>Soba Dipping Sauce</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Snack</strong></td>
<td><strong>Snack</strong></td>
<td><strong>Snack</strong></td>
<td><strong>Snack</strong></td>
<td><strong>Snack</strong></td>
</tr>
<tr>
<td>Tangerines</td>
<td>Apple</td>
<td>Raisins &amp; Melons</td>
<td>Pears</td>
<td>Apple</td>
</tr>
<tr>
<td>Carrot Juice</td>
<td></td>
<td>Vegetable Juice</td>
<td>Carrot Juice</td>
<td>Vegetable Juice</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
Physiological Responses to Different Diets among Asian Americans (N=23)

<table>
<thead>
<tr>
<th></th>
<th>Asian Diet</th>
<th>P-value(^1)</th>
<th>Western Diet</th>
<th>P-value(^2)</th>
<th>P-value(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ΔV3-V2</td>
<td></td>
<td>ΔV4-V3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>-1.8 ± 1.6</td>
<td>&lt;0.001</td>
<td>0.3 ± 0.9</td>
<td>0.131</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body Mass Index (BMI)(^{kg/m^2})</td>
<td>-0.6 ± 0.6</td>
<td>&lt;0.001</td>
<td>0.1 ± 0.3</td>
<td>0.283</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body Fat %</td>
<td>-1.5 ± 1.6</td>
<td>&lt;0.001</td>
<td>0.7 ± 1.2</td>
<td>0.016</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Trunk Fat %</td>
<td>-2.1 ± 2.0</td>
<td>&lt;0.001</td>
<td>0.9 ± 1.8</td>
<td>0.019</td>
<td>0.001</td>
</tr>
<tr>
<td>Insulin AUC(^{μU/mL\cdot120 \text{ min}})</td>
<td>-1402.4 ± 2320.8</td>
<td>0.017</td>
<td>606.2 ± 1898.9</td>
<td>0.232</td>
<td>0.015</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>-0.3 ± 0.8</td>
<td>0.099</td>
<td>0.2 ± 0.7</td>
<td>0.232</td>
<td>0.042</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td>-23.9 ± 23.7</td>
<td>0.001</td>
<td>17.9 ± 20.5</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>-9.5 ± 9.4</td>
<td>0.001</td>
<td>6.2 ± 7.1</td>
<td>0.002</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>-14.0 ± 21.3</td>
<td>0.005</td>
<td>5.8 ± 14.8</td>
<td>0.054</td>
<td>0.014</td>
</tr>
<tr>
<td>Adiponectin (ng/mL)</td>
<td>-1071.8 ± 5947.3</td>
<td>0.520</td>
<td>1344.7 ± 7465.1</td>
<td>0.370</td>
<td>0.205</td>
</tr>
<tr>
<td>Leptin (ng/mL)</td>
<td>-2.2 ± 3.7</td>
<td>0.014</td>
<td>1.6 ± 3.3</td>
<td>0.016</td>
<td>0.012</td>
</tr>
<tr>
<td>PAI-1 (ng/mL)</td>
<td>-13.4 ± 30.4</td>
<td>0.012</td>
<td>-8.7 ± 53.0</td>
<td>0.218</td>
<td>0.027</td>
</tr>
<tr>
<td>Isoprostane (ng/mL)</td>
<td>0.1 ± 1.8</td>
<td>0.664</td>
<td>0.9 ± 1.7</td>
<td>0.014</td>
<td>0.590</td>
</tr>
</tbody>
</table>

\(^1\) P-value of the changes observed before and after 8 weeks of TAD (v3-v2)

\(^2\) P-value of the changes observed before and after 8 weeks of TWD (v4-v3)

\(^3\) P-value of the v4-v3 and v3-v2
Strategy 2: Reduce Your Body Weight by 5 to 7 Percent
Difference in diabetes prevalence at different BMI

Figure 1—Diabetes risk by BMI category in the Hawaii component of the Multiethnic Cohort Study. The reference group is Caucasians in the lowest BMI category.
Figure 2

Figure shows mean (±SE) weight losses over 8 years for participants randomly assigned to an intensive lifestyle intervention (ILI) or diabetes support and education (DSE; usual care group). Differences between groups were significant (p<0.001) at all years.
Diabetes Prevention Program among Chinese

Strategy 3: Increase Your Muscles’ Glucose-Absorbing Ability Through Aerobic Exercise and Strength Training
Physical exercise is critical in the prevention and treatment of type 2 diabetes.

Regular physical exercise is essential for overall health.
Effect of Exercise on Blood Glucose Concentrations in Subjects with Type 2 Diabetes

![Graph showing the effect of exercise on blood glucose concentrations. The graph shows a decrease in glucose levels from basal to 75 minutes of exercise at 70% VO$_{2}$max.](image)
Strategy 4: Activate Your Brown Fat (Why Not All Fat Is Bad For You)
Not all fat are bad
There are white fat, brown fat
And beige fat.
Two Types of Fat – and Brown is “Good”

White (WAT)

- Energy storage
  - 50g contains 300-500 kcal

- Cold-induced [NST]

- Diet-induced [DIT]

Brown (BAT)

- Energy expenditure
  - 50g consumes 100-300 kcal/day (max)

Where are the brown and beige fat depots?

Jespersen NZ et al. Cell Metabolism 2013;17:798

Outline from http://selfcarerevival.blogspot.com/2012_05_01_archive.html
In Summary

- Pediatric BAT activity peaks in adolescence and, like adult BAT, may have a role in obesity.
- BAT can be found in a substantial proportion of adult humans (≤100%), and preliminary data suggest that it could consume up to 100-200 kcal per day with activation.
- Treating obesity and diabetes by increasing BAT energy expenditure has great potential.
- BAT and beige fat are activated and induced by cold temperature around 62 °F.
- May be we should exercise in room around 62-65 °F.
Strategy 5: Become an Inflammation Fighter
Prevalence of Elevated Serum C-Reactive Protein Concentration by BMI Category in Men and Women Aged 17 Years or Older* (NHANES III)

*Normal weight was considered a body mass index (BMI) of less than 25 kg/m²; overweight, 25–29.9 kg/m²; and obese, 30 kg/m² or more.

Therapeutic Interventions Which Modulate Inflammation

- Low Fat Diet/ Weight Loss
- Insulin Sensitizers
- Insulin
- Statin Therapy
- TNF Receptor Antagonist
- IL1 Receptor Antagonist
- Salicylates
Anti-inflammatory Foods
TINSAL-T2D Stage 2: Salsalate Trial

HbA1c (primary endpoint)

Mean change in HbA1c (%)

Placebo

Salsalate

Goldfine et al, Ann Int Med, 2010
Strategy 6: Get 7 to 8 Hours of High-Quality Sleep Every Night
Sleeping Pattern Over Years

Americans are sleeping less than they used to

Source: Gallup
Americans with insufficient sleep or obesity

- Less than 7 hours sleep per work night: 37.1%
- Obesity: 35.7%

Source: CDC
<table>
<thead>
<tr>
<th></th>
<th>≤6 h per night (n=90)</th>
<th>7–8 h per night (n=571)</th>
<th>≥9 hours per night (n=149)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OR</strong></td>
<td>2.02</td>
<td>1.00</td>
<td>1.46</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>1.32–3.23</td>
<td>0.95–2.14</td>
<td>0.91–2.09</td>
</tr>
<tr>
<td><strong>Reference</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Model 1</strong></td>
<td>1.80</td>
<td>1.46</td>
<td>0.91–2.09</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>1.15–2.98</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Model 2</strong></td>
<td>1.76</td>
<td>1.35</td>
<td>0.83–1.99</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>1.08–2.84</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Model 3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td></td>
<td></td>
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</tbody>
</table>

1. Metabolic syndrome defined according to the American Heart Association/National Heart, Lung, and Blood Institute’s criteria [31].

Model 1: unadjusted odds ratio.
Model 2: adjusted for age, sex, smoking habits, highest education level, total annual family income, alcohol consumption, coffee intake, and menopausal status.
Model 3: adjusted for daily caloric intake and moderate-to-vigorous physical activity in addition to age, sex, smoking habits, highest education level, total annual family income, alcohol consumption, coffee intake, and menopausal status.

Abbreviations: OR, odds ratio; CI, confidence interval.
Strategy 7: Reduce Stress and Manage Your Mental Health
DM prevalence and Traditional Mode of Acculturation in Kanaka `Oiwi

![Prevalence of Diabetes by Acculturation Modes](image-url)
Strategy 8: Boost Your Own Natural Antioxidants
Anti-oxidant Foods
Results of the HOPE Trial

Lonn, E et al, Diabetes Care 25: 1919, 2002
Activate Nrf2: Switch on endogenous antioxidant system

Geismann, et al. 2014
Onco Targets Ther. 7:1497-518.
The Eight Strategies For Avoiding, Controlling, or Reversing Diabetes

Strategy 1 The Rural Asian Diet (RAD) Eating Plan: Cut Your Fat Intake in Half and Double Your Fiber

Strategy 2 Reduce Body Weight by 5 Percent – reduce portion size

Strategy 3 Increase Your Muscles’ Glucose-Absorbing Ability - Aerobic Exercise and Strength Training

Strategy 4 Activate Your Brown Fat – exercise in cool room.

Strategy 5 Become an Inflammation Fighter - food, activities and medications

Strategy 6 Sleep 7 to 8 Hours of High-Quality Sleep Every Night

Strategy 7 Reduce Stress

Strategy 8 Boost Your Own Antioxidants – green veggies
• Personalize these steps into your life and they will enhance your life’s enjoyment.
Acknowledgements

• AADI Team: Karen Lau, CDE, William Hsu, MD
• DPP study: Edward Horton, MD
• Exercise: Lurie Goodyear, PhD
• Inflammation: Drs. Allison Goldfine and Steve Shoelson
• Brown fat: Drs. Aaron Cypess and Ron Kahn
• Antioxidants and NRF2: Dr. Keith Blackwell