Exercise and Type 2 Diabetes (T2D)

Judith G. Regensteiner, PhD
Professor of Medicine
Director, Center for Women’s Health Research
University of Colorado Denver School of Medicine
• I have no conflicts of interest to declare
Diabetes: The problem

• Nearly 22 million people have diabetes; 90% of these have type 2 diabetes, 10% type 1 diabetes
• One of the only diseases increasing in prevalence in the Western world
• Increasing prevalence in the elderly
Diabetes: A Major Risk Factor for Heart Disease

• Majority of people with T2D have additional risk factors for heart disease
• 2 out of 3 people with T2D die of some type of cardiovascular disease (CVD)
• Aggressive therapy for diabetes and high blood pressure is usually needed
• Diabetes causes decrease in ability to exercise

Mortality Due to Heart Disease in Men and Women with or without Diabetes (US)

*Age-adjusted. Individuals categorized at NHANES I: 1971-75; F/U 1992-1993
Adapted from Gu K et al. Diabetes Care 1998;21:1138-1145.
Physical Inactivity: Vicious Cycle

Sedentary Lifestyle → Insulin resistance → Obesity/Type 2 Diabetes → Defective Exercise Capacity
Exercise for T2D

- **American Diabetes Association**
  - “the possible benefits of exercise in type 2 diabetes are substantial”

- **American College of Sports Medicine**
  - “physical activity is a major therapeutic modality for type 2 diabetes”
Type 2 diabetes may be thwarted

Study: Exercise, diet a prevention

By Allison Sherry
Denver Post Staff Writer

A gradual lifestyle change including moderate exercise and a low-fat diet may prevent the most common form of diabetes, Colorado researchers have found in the world’s first study on diabetes that included a large portion of minority participants.

“We’re not curing it; we’re preventing it,” said Dr. Richard Hamman, who works in preventive medicine and biometrics at the University of Colorado Health Sciences Center. The study included 3,224 people nationwide; 66 percent of them were people of color, who were thought to be high-risk for Type 2 diabetes. This form of the disease usually sets in later in life and is caused by obesity.

About 16 million Americans have the disease; 286,000 of them live in Colorado. The disease was once thought to hit mostly adults, but an alarmingly high number of children have been diagnosed with it in recent years — mostly because of an increase in sluggish lifestyles.

One-third of the study’s participants took blood-sugar-lowering medication, another third took a placebo and the last third changed their eating habits and lowered their body fat by walking 150 minutes a week.

Study finds that diet and exercise may prevent Type 2 diabetes

DIABETES from Page 18

Researchers found that the exercising group lost weight and decreased chances of getting diabetes by 38 percent.

“We’re not talking about huge changes. We’re talking about a 5 to 7 percent weight loss,” said Dr. Ned Colange, chief of prevention at Kaiser Permanente.

Colange thinks the exercise could almost be completely prevented with a combination of metformin and lifestyle change.

Doctors didn’t chronicle anyone doing both, but some participants, including 40-year-old Denver resident Henriette Wabukuma, did a little exercise on their own. Wabukuma participated in the study because she knew type 2 diabetes ran in her family. She saw family members who had to make drastic changes to their diet and take medication — and she didn’t want to do that.

Wabukuma, who was a part of the group taking metformin, said she tried to exercise a little during the study but wants to try harder now that she knows the dramatic difference it can make in feeling well. Plus, she doesn’t want to take pills on a daily basis.

“Lifestyle changes are something I would like to try,” said Wabukuma, a lab technician at Quest Diagnostics. “It would be hard. But for me, I don’t like to take a pill every day.”

Exercise, Weight Loss Can Delay Diabetes

By Sally Squires
Washington Post Staff Writer

At least 10 million overweight Americans could sharply cut their risk of developing diabetes by making relatively simple lifestyle changes in their diets and exercise routines, according to a major government study released yesterday.

The Diabetes Prevention Program is the largest study to show that losing weight and exercising can effectively delay diabetes in a wide range of overweight men and women who are at a high risk.

Please see DIABETES on 78

The Washington Post

Thursday, August 9, 2001

Weather

Today: Sunny, hot, humid.
High 90, Low 78.

Thursday: Partly sunny, humid.
High 84, Low 76.

Details, Page B8

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Final
Cardiovascular Fitness and Mortality

- Low cardiorespiratory fitness predicted CVD and all cause mortality in healthy men
  - 25,714 people evaluated prospectively
  - True whether normal weight, overweight or obese

- In men with DM, low CV fitness and physical inactivity predicted mortality
  - 1,263 people in a preventive medicine clinic

**Figure.** Survival curves for all-cause mortality by cardiorespiratory fitness category. Data are from 1263 men with 180 all-cause deaths during 14,777 man-years of observation. The solid line represents fit participants and the dashed line represents unfit participants.

Church 2005; Lyerly et al. 2009
Exercise and T2D

- Exercise is cornerstone of prevention and treatment for T2D but exercise capacity very reduced in diabetes
  - patients may experience discomfort during exercise-this is a disincentive
  - most people with T2D are sedentary
  - Exercise performance may be worse in women with T2D than men with T2D
    - Causes for this are unknown
“Will I still be able to not exercise?”
Baseline Abnormalities in Exercise Performance in T2D

• Reduced maximal oxygen consumption
  – gold standard for cardiopulmonary function

• Slowed oxygen uptake kinetics (marker for submaximal exercise levels)
  – Clinically relevant marker of cardiovascular fitness
Exercise Duration and VO$_2$max in T2D

**Exercise Duration**

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 min</td>
<td>15 ml/kg/min</td>
<td>20 ml/kg/min</td>
</tr>
<tr>
<td>20 min</td>
<td>20 ml/kg/min</td>
<td>25 ml/kg/min</td>
</tr>
</tbody>
</table>

**VO$_2$max**

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 min</td>
<td>25 ml/kg/min</td>
<td>30 ml/kg/min</td>
</tr>
<tr>
<td>20 min</td>
<td>30 ml/kg/min</td>
<td>35 ml/kg/min</td>
</tr>
</tbody>
</table>

* = p < 0.05

Regensteiner et al., Diabetes Care 1999
What causes the abnormalities?

Are causes:  
Peripheral?  
Central?
## Demographic Variables

<table>
<thead>
<tr>
<th></th>
<th>Controls (N=10)</th>
<th>Type 2 Diabetes Mellitus (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>39.3 ± 6.6</td>
<td>42.5 ± 6.3</td>
</tr>
<tr>
<td><strong>Duration of Diagnosed Diabetes (years)</strong></td>
<td>------</td>
<td>3.6 ± 4.6</td>
</tr>
<tr>
<td><strong>Body Mass Index (kg/m²)</strong></td>
<td>28.3 ± 3.9</td>
<td>31.9 ± 4.3</td>
</tr>
<tr>
<td><strong>HbA1C (%)</strong></td>
<td>5.0 ± 0.4</td>
<td>6.9 ± 2.3*</td>
</tr>
<tr>
<td><strong>Total Cholesterol</strong></td>
<td>194 ± 33</td>
<td>188 ± 20</td>
</tr>
<tr>
<td></td>
<td>Controls (N=10)</td>
<td>T2D (N=10)</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-----------------</td>
<td>------------</td>
</tr>
<tr>
<td>VO$_2$ max (ml/kg/min)</td>
<td>22.3±4.2</td>
<td>18.7±2.3*</td>
</tr>
<tr>
<td>VO$_2$ max (ml/min)</td>
<td>1639.9±336.8</td>
<td>1519.8±248.6</td>
</tr>
<tr>
<td>Respiratory Exchange Ratio</td>
<td>1.14±0.05</td>
<td>1.18±0.05</td>
</tr>
<tr>
<td>Rate of Perceived Exertion</td>
<td>17.1±1.4</td>
<td>16.6±1.8</td>
</tr>
<tr>
<td>Watts</td>
<td>123±27.5</td>
<td>110±21.1</td>
</tr>
<tr>
<td>HR max (beats/min)</td>
<td>166±15</td>
<td>169±8</td>
</tr>
<tr>
<td>Cardiac Output (Fick) (L/min)</td>
<td>13.1±2.8</td>
<td>12.6±1.6</td>
</tr>
<tr>
<td>Cardiac Index (L/min)(Fick)</td>
<td>7.3±1.4</td>
<td>6.8±0.5</td>
</tr>
<tr>
<td>Arteriovenous oxygen difference</td>
<td>12.8±2.2</td>
<td>12.3±1.3</td>
</tr>
<tr>
<td>Right Atrial Pressure (mmHg)</td>
<td>10.8±3.1</td>
<td>10.7±3.8</td>
</tr>
<tr>
<td>Mean Arterial Pressure (mmHg)</td>
<td>107.6±7.3</td>
<td>117.7±12.6*</td>
</tr>
<tr>
<td>Pulmonary Arterial Pressure (mmHg)</td>
<td>30.3±6.7</td>
<td>34.0±1.5</td>
</tr>
<tr>
<td>Pulmonary Capillary Wedge Pressure (mmHg)</td>
<td>16.7±3.7</td>
<td>23.6±3.9*</td>
</tr>
</tbody>
</table>

Regensteiner et al  Medicine, Science, Sport and Exercise 2009
T2D has adverse effects on cardiac function
(Regensteiner et al. 2009)
### Nuclear stress (Tc-99m sestamibi) tests

<table>
<thead>
<tr>
<th></th>
<th>Controls (N=7)</th>
<th>Type 2 Diabetes Mellitus (N=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>41±7</td>
<td>43±6</td>
</tr>
<tr>
<td>BMI</td>
<td>28.3±3.2</td>
<td>32.1±5.2</td>
</tr>
<tr>
<td>Total Rest Counts</td>
<td>493.1±138.4</td>
<td>420.0±106.7</td>
</tr>
<tr>
<td>Total Stress Counts</td>
<td>834.8±216.4</td>
<td>656.9±139.4+</td>
</tr>
<tr>
<td>Total Perfusion Reserve (ratio)</td>
<td>1.66±0.33</td>
<td>1.44±0.22</td>
</tr>
<tr>
<td>Resting LV Mass</td>
<td>138.6±22.3</td>
<td>138.1±18.2</td>
</tr>
<tr>
<td>Stress counts/resting myocardial mass</td>
<td>6.60±2.15</td>
<td>4.28±0.75*</td>
</tr>
<tr>
<td>Total myocardial perfusion index</td>
<td>17.5±8.1E-9</td>
<td>11.0±3.5xE-9 *</td>
</tr>
</tbody>
</table>
What about T2D in youth?

- Growing problem
- Related to increased obesity/sedentary behavior in adolescents
Insulin Resistance in Adolescents with T2D is Associated with Impaired Exercise Capacity

Nadeau KJ et al. J Clin Endocrinol Metab. 2009
RESULTS: Youth with T2D have elevated triglycerides, free fatty acids, CRP and low adiponectin, not seen in T1D

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Obese</th>
<th>T2D</th>
<th>T1D</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>12</td>
<td>13</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Age (years)</td>
<td>15.6</td>
<td>1.8</td>
<td>14.9</td>
<td>2.1</td>
</tr>
<tr>
<td>Tanner Stage</td>
<td>4.4</td>
<td>0.7</td>
<td>4.6</td>
<td>0.6</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>21</td>
<td>2.4</td>
<td>32</td>
<td>5.4*</td>
</tr>
<tr>
<td>HbA-1c (%)</td>
<td>4.9</td>
<td>0.3</td>
<td>5</td>
<td>0.3</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>82</td>
<td>37</td>
<td>211</td>
<td>168%</td>
</tr>
<tr>
<td>FFA (uEq/L)</td>
<td>409</td>
<td>181</td>
<td>583</td>
<td>144%</td>
</tr>
<tr>
<td>hs CRP (mg/L)</td>
<td>0.8</td>
<td>0.8</td>
<td>1.12</td>
<td>1.5</td>
</tr>
<tr>
<td>Adiponectin (ug/ml)</td>
<td>8.4 ± 4.1</td>
<td>9.9</td>
<td>3.3</td>
<td>6.4</td>
</tr>
</tbody>
</table>

*p<0.0001 vs control, %p=0.01 vs control, &p<0.04 vs control (Nadeau et al JCEM in press)
Peak Oxygen Consumption

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Obese</th>
<th>T2D</th>
<th>T1D</th>
</tr>
</thead>
<tbody>
<tr>
<td>3DPAR</td>
<td>1.8</td>
<td>1.7</td>
<td>1.8</td>
<td>1.8</td>
</tr>
<tr>
<td>RER</td>
<td>1.18</td>
<td>1.13</td>
<td>1.13</td>
<td>1.15</td>
</tr>
<tr>
<td>Peak Heart Rate</td>
<td>184</td>
<td>188</td>
<td>183</td>
<td>177</td>
</tr>
</tbody>
</table>

Nadeau et al JCEM in press

*p<0.04 vs. controls, #p<0.01 vs. controls, ^p<0.04 vs. obese and T1D
Insulin sensitivity

Glucose Disposal

**Nadeau et al JCEM in press**

* *p<0.001 vs. control, ^p<0.01 vs. T1D and obese*
Results: Correlations

$\text{VO}_2\text{max/kg}$ correlated positively with insulin sensitivity (mg/kg/min) ($r=0.82$, $p<0.0001$)

Nadeau et al JCEM in press
Does exercise training benefit T2D?
Physical activity is beneficial for reducing mortality in T2D

- 3316 persons ages 25-74 years with type 2 diabetes
- Survey between 1972 and 1997 on physical activity, smoking, medical history
- Average follow-up was 18 years
- 1410 died during follow-up, 903 died of CVD
- Physical during work, leisure time, and commuting defined as light, moderate, hard

Most exercise studies show improved glycemic control from exercise training

Meta-analysis of 14 exercise trials showed a \(0.66\%\) reduction in hemoglobin \(A_{1c}\)

*JAMA* 2001;286:1218-1227
Exercise Capacity Improves with Exercise Training

<table>
<thead>
<tr>
<th></th>
<th>Lean Control</th>
<th>Obese Control</th>
<th>DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>36±6</td>
<td>37±6</td>
<td>42±7</td>
</tr>
<tr>
<td>Fat Free Mass (kg)</td>
<td>42±7</td>
<td>48±5</td>
<td>47±5</td>
</tr>
<tr>
<td>HgbA1c</td>
<td>6.0±0.6</td>
<td>5.3±0.5</td>
<td>9.0±0.4*</td>
</tr>
</tbody>
</table>

Maximal Exercise Response: exercise training program

<table>
<thead>
<tr>
<th></th>
<th>Lean Control</th>
<th>Obese Control</th>
<th>DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO₂peak (pre)</td>
<td>25.7±4.9</td>
<td>21.8±2.3</td>
<td>17.3±3.8</td>
</tr>
<tr>
<td>(post)</td>
<td>27.9±5.3*</td>
<td>23.0±2.9*</td>
<td>21.7±5.6*</td>
</tr>
<tr>
<td>Maximal RER</td>
<td>1.13±0.05</td>
<td>1.13±0.08</td>
<td>1.16±0.11</td>
</tr>
</tbody>
</table>

(no significant change with training)

Regensteiner, Diabetes Care 22.1640-1646, 1999
CV adaptations to exercise training in postmenopausal women with T2D

- Women with T2DM, age 59±7 yrs, randomly assigned to 10 weeks of exercise (n=17) vs control (n=7)
- Measures were peak oxygen uptake, LV filling dynamics, arterial compliance, lipids, insulin sensitivity
- Exercise: 3/week, 10 weeks, aerobic and resistance training

Cardiovascular Diabetology 2004, 3:3
CV adaptations to exercise training in postmenopausal women with T2D

• Among exercisers:
  – Peak oxygen uptake increased by 15%, P<0.05
  – Large artery compliance increased from 1.0 ± 0.4 to 1.2 ± 0.4 ml/mm Hg, P<0.05
  – No changes in other variables

• Among controls, no significant changes in any variable

• Exercise training improves large artery compliance and CV fitness in postmenopausal women with diabetes, without appreciable changes in LV filling dynamics or risk factors for CVD
Why does exercise improve exercise abnormalities in T2D?
Mechanisms by Which Exercise Training May Improve Cardiovascular Health in Persons with T2D

**Exercise Training**

- Increases aerobic capacity and muscle strength
- Effective, good evidence
- Potential, not yet proven
- Reduces total body and visceral fat; increases lean mass
- Lowers blood glucose; increases insulin sensitivity
- Reduces blood pressure
- Reduces left ventricular mass
- Subendocardial ischemia; ischemic preconditioning
- Increased nitric oxide production
- Improves endothelial vasodilator function
- Improves left ventricular diastolic function
- Decreases arterial stiffness
- Attenuates systemic inflammation

Increases aerobic capacity and muscle strength

Exercise Training

Effective, good evidence

Potential, not yet proven

Increases aerobic capacity and muscle strength
Endothelial Function
Acute episodes of exercise increases blood flow and the resulting shear stress stimulates production of nitric oxide synthase leading to smooth muscle relaxation.

Exercise training exposes the vessels to a series of repeated episodes of hyperemia. The chronically elevated shear stress increases the vascular expression of nitric oxide synthase, thereby enhancing the release of nitric oxide, leading to a greater capacity for vasodilation.
Endothelial vasodilator function and exercise training in type 2 diabetes

- Randomized cross over trial; patients with type 2 diabetes; aged 52± 2 yrs; n=16
- Patients performed 3 weekly 1-hour sessions of moderate-intensity aerobic and resistance training for 8 weeks
- Brachial artery flow-mediated dilation increased from 1.7 % to 5%

*P<0.001

J Am Coll Cardiol 2001;38:860-866
# Exercise and Endothelial Vasodilator Function

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Exercise Protocol</th>
<th>Endothelial Function Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT; asymptomatic men, aged 40 to 60 yrs, with metabolic syndrome; n=29; <em>Arterioscler Thromb Vasc Biol</em> 2000;20:551-555</td>
<td>12 weeks; 3 weekly sessions of cycling; 20 minutes of warm up; 30 minutes at 80% of maximal HR</td>
<td>Reactive hyperemic brachial artery flow mediated dilation increased from 5.3% to 7.3%</td>
</tr>
<tr>
<td>RCT; subjects with and without untreated mild hypertension; aged 47± 10 yrs; n=17; <em>Circulation</em> 1999;100:1194-1202</td>
<td>12 weeks; 30 minutes of brisk walking, 5 to 7 times per week</td>
<td>Endothelium-dependent forearm blood flow increased by 25% in subjects with and without hypertension</td>
</tr>
<tr>
<td>RCT; subjects with mild essential hypertension; aged 53± 10 yrs; n=27; <em>Hypertension</em> 1999;33: S1, S91 S97</td>
<td>12 weeks; 30 minutes of brisk walking, 5 to 7 times per week</td>
<td>Reactive hyperemic endothelium-dependent forearm blood flow increased by 25%</td>
</tr>
</tbody>
</table>
Prescription for Exercise
Physical Activity Guidelines
Advisory Committee Report 2008
To the Secretary of Health and Human Services

www.health.gov/paguidelines
2008 Physical Activity Guidelines
Advisory Committee Report

Strong evidence for benefit with respect to:

- All-cause mortality
- CHD
- Blood pressure
- Stroke
- Type 2 diabetes
- Metabolic syndrome
- Colon cancer
- Breast cancer
- Depression
- Functional health
- Falls
- Cognitive function

Recommendations Before 1995
“No Pain, No Gain” Era

- Vigorous exercise (e.g., jogging or running) for at least 20 minutes continuously, 3X/week
- E.g., recommendations from ACSM and AHA, 1970’s to early 1990’s
Recommendations After 1995

• Accumulate at least 30 min/day of moderate-intensity physical activity (e.g., brisk walking), most days
• First issued by CDC/ACSM in 1995
• Similar recommendations subsequently from various organizations
2008 DHHS Physical Activity Guidelines for Adult Americans

- Adults who participate in any amount of physical activity gain some health benefits.
- A total of 2 hours and 30 minutes (150 minutes) a week of moderate-intensity aerobic activity substantially reduces the risk of many chronic diseases and other adverse health outcomes.
- As a person moves from 2 hours and 30 minutes (150 minutes) a week toward 5 hours (300 minutes) a week, he or she gains additional health benefits.
- Muscle-strengthening activities involving all major muscle groups should be performed on 2 or more days a week.
Guidelines for Exercise: T2D

- Patients with diabetes should exercise as part of their medical management.
- There is good evidence to suggest benefits of exercise training extend to the cardiovascular consequences of these diseases.
Exercise Stress Testing

Exercise heart rate blood pressure responses provide data for an exercise prescription.
Indications for Cardiac Testing in Patients with Diabetes

- Typical or atypical cardiac symptoms
- Resting ECG suggestive of ischemia or infarction
- Peripheral or carotid occlusive arterial disease
- Sedentary lifestyle or plan to begin a vigorous exercise program
- Two or more of the risk factors listed below
  - Total cholesterol ≥240 mg/dL, LDL cholesterol ≥160 mg/dL, or HDL cholesterol <35 mg/dL
  - Blood pressure >140/90 mmHg
  - Smoking
  - Family history of premature CAD
  - Positive micro/macroalbuminuria
Exercise and Type 2 Diabetes: The American College of Sports Medicine and the American Diabetes Association: joint position statement

- Sheri Colberg, PhD
- Ronald Sigal, MD MPH,
- Bo Fernhall, PD
- Bryan Blissmer PhD,
- Richard Rubin, PhD
- Judith Regensteiner, PhD
- Lisa Chasan-Taber, PhD
- Ann Albright, PhD
- Barry Braun PhD
- Colberg et al, 2010, Diabetes Care and MSSE.
Pre-exercise Evaluation

• Before undertaking exercise more intense than brisk walking, sedentary persons with T2D will likely benefit from an evaluation by a physician. ECG exercise stress testing for asymptomatic individuals at low risk of CAD is not recommended but may be indicated for higher risk. C/C
Exercise Prescription

• Types and frequency of exercise
  – Aerobic type 5 times a week
  – Resistance exercise 2 times a week

• Intensity
  – Aerobic exercise at 55% to 85% of maximal HR
  – Resistance exercise at 30% to 50% of 1-repetition maximum, 12-15 repetitions, 8 to 10 different exercises
  – Energy expenditure >1000 kilocalories per week

• Duration
  – Aerobic for 30 to 45 minutes
  – Resistance takes about 20 minutes
Exercise Precautions

• Medical therapy should be initiated before exercise training if SBP ≥ 160 mm Hg or DBP ≥ 100 mm Hg

• Hypoglycemic reactions in type 2 diabetes are rare
  – Extra carbohydrates may be needed for events > 60 minutes

• Exercise contraindications based on resting blood glucose levels are not definitive
  – 60 mg/dL to 300 mg/dL or 400 mg/dL generally recommended for avoiding hypoglycemia and ketosis

• Extended breath-holding should be avoided to minimize excessive blood pressure responses

• Exercise does not worsen diabetic retinopathy and may delay eye complications by reducing atherosclerotic risk
  – Heavy straining should be avoided
Summary

• Exercise is critical for prevention of both diabetes and death
• People with diabetes have defects in functional exercise capacity
• Effects of exercise on the heart and vasculature are still to be defined
Walking shoes are 80 bucks
A triple bypass - 80 grand
Think of all that cash in hand
And march that tush along the land.
Thank you
Thanks!!!

• Jane Reusch, MD
• Kristen Nadeau, MD
• Amy Huebschmann, MD
• Irene Schauer, MD, PhD
• Tim Bauer, PhD
• Ryan Mays, PhD
• Jordan Thomas, MS

• Leah Herlache, MA
• Sarah Gilligan, MA
• Lisa Herbert, MA
• Melanie Cree Green, MD, PhD