UNDERSTANDING THE SPEED OF AGING IN ADULTS WITH CEREBRAL PALSY.

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University of Michigan-Medicine
Department of Physical Medicine & Rehabilitation
Speaker Names: Edward A. Hurvitz, MD and Mark D. Peterson, PhD

Disclosure of Relevant Financial Relationships
We have no financial relationships to disclose.

Disclosure of Off-Label and/or investigative uses:
We will not discuss off label use and/or investigational use in my presentation.
Agenda

• Dr. Hurvitz:
  – Patient case-studies to demonstrate the issues related to functional loss, pain, diminished quality of life, and frustration pertaining to lack of life-course and lifespan approaches.
  – The progression of a non-progressive condition: Losses of function during the transition into and throughout adulthood

• Dr. Peterson:
  – New findings on risk factors for chronic disease and multimorbidity, and associations with hallmark function and symptom phenotyping in CP.
  – New findings pertaining to longitudinal trajectories and disease free survival of chronic diseases in CP.

• Open Forum and Q&A
Aging with a disability: Fitness and Function

Pediatric Onset Disability

Muscle, Bone Limb, Joint Development

Accessibility of gyms
Lack of information

Walking, Running, Movement affected

Decreased activity, exercise

No life pattern of activity
Social skills
• Most common childhood onset physical disability
  – About 3/1,000 births*
• Primary condition non-progressive
• Life span to adult years, normal in less affected (GMFCS I-III)
• Estimate 500,000 adults with CP in USA

Function

- Functional status as child predicts adulthood
- Decline is frequently, but not always seen
- Decline may relate to secondary factors
  - Decreased aerobic capacity/fitness
  - Musculoskeletal dysfunction
  - Pain
  - Fatigue
Well described pattern

- Opheim, 2009, DMCN
  - 7 year f/u on 1999 study
  - Reports of decreased walking function increased
    - 39% to 52%
    - Includes 37% with hemiplegia
    - Age of change
      - 37 years old for bilateral
      - 52 for unilateral
    - Associated with reports of pain and fatigue
• Struggles with weight issues
• Low bone density, high cholesterol
• All mobility with walker, does not own chair
• Musculoskeletal pain—Shoulders, Wrists, Hips, painful feet
• High fatigue, Limited participation
• Talked about power mobility
• “Feels like a failure...”
- Military Service! Made it into the Navy
- Always had a high fitness level, worked out with SEALS
- Fatigue, less able to participate
- BMI normal, High WHR
- Cholesterol high, HDL Low
- Not sleeping well
### Patient Information

- **ID:** 101
- **Birth Date:** 4/18/1962
- **Age:** 45.2 years
- **Height:** 75.0 in.
- **Weight:** 196.0 lbs.
- **Sex:** Male
- **Ethnicity:** White

### Facility Information

- **Facility ID:** 2137-Drs. Hurvitz
- **Referring Physician:** Dr. Hurvitz
- **Date of Referral:** 7/13/2007
- **Time of Referral:** 8:52:58 AM
- **Date of Analysis:** 7/13/2007
- **Time of Analysis:** 9:27:38 AM

### Composition Reference: Total

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Tissue (%Fat)</th>
<th>Centile</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>40</td>
<td>10</td>
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</tr>
<tr>
<td>50</td>
<td>15</td>
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<tr>
<td>60</td>
<td>20</td>
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<tr>
<td>70</td>
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<tr>
<td>80</td>
<td>30</td>
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<tr>
<td>90</td>
<td>35</td>
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</tr>
<tr>
<td>100</td>
<td>40</td>
<td>40</td>
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</table>

### Composition Trend: Total Fat Free (g)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Fat Free (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>44</td>
<td>63730</td>
</tr>
<tr>
<td>45</td>
<td>63729</td>
</tr>
<tr>
<td>46</td>
<td>63728</td>
</tr>
<tr>
<td>47</td>
<td>63725</td>
</tr>
</tbody>
</table>

### Trend: Total

<table>
<thead>
<tr>
<th>Measured Date</th>
<th>Age (years)</th>
<th>Tissue (%Fat)</th>
<th>Centile</th>
<th>T. Mass (kg)</th>
<th>Region (%Fat)</th>
<th>Tissue (g)</th>
<th>Fat (g)</th>
<th>Lean (g)</th>
<th>BMC (g)</th>
<th>Fat Free (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7/13/2007</td>
<td>45.2</td>
<td>28.7</td>
<td>91</td>
<td>88.1</td>
<td>27.7</td>
<td>84,928</td>
<td>24,369</td>
<td>60,559</td>
<td>3,169</td>
<td>63,725</td>
</tr>
</tbody>
</table>

### Trend: Fat Distribution

<table>
<thead>
<tr>
<th>Measured Date</th>
<th>Age (years)</th>
<th>Android (%Fat)</th>
<th>Gynoid (%Fat)</th>
<th>A/G Ratio</th>
<th>Total Body (%Fat)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7/13/2007</td>
<td>45.2</td>
<td>39.4</td>
<td>32.4</td>
<td>1.22</td>
<td>28.7</td>
</tr>
</tbody>
</table>

### World Health Organization BMI Classification

- Body Mass Index (BMI) = 24.5
- **Underweight:** 10
- **Normal:** 18.5
- **Overweight:** 25
- **Obesity:** 30

![BMI Classification Chart](chart.png)
CD, 26 year old, GMFCS III

- Four months ago
  - ADL Independent, Ambulatory with crutches
  - Driving Working

- NOW
  - Fully dependent, can barely stand
  - Joint pain...with swelling

- Many Doctors—”CP getting worse...”
Children with QCP have more IMAT than typically developing children, and was found to be related to their low level of physical activity. Johnson et al. J Pediatr. 2009 May;154(5):715-20.

Separation of AT from MRI of the midthigh of a prepubertal girl with QCP and D-F, a typically developing prepubertal girl. A and D contain subcutaneous, subfascial, and intermuscular AT; B and E contain only subfascial and intermuscular AT; and C and F contain only IMAT.

Not just a factor of aging and obesity.
T1-weighted MRI from the mid-tibia demonstrate the marked deficit in bone architecture and muscle volume and the high infiltration of fat within and around the musculature in an ambulatory boy with mild CP (A) compared to a typically developing boy with the same tibia length (B).

• What happens to children, adolescents, and young adults with CP as they transition throughout adulthood?

• Contemporary jargon:
  – Accelerated aging
  – Premature frailty phenotype
  – Normal weight obesity
  – Exaggerated sedentariness
My Current Focus: Predictors, Confluence and Consequences of Frailty and Obesity in Cerebral Palsy

- Sedentary Behavior
- High Fat Diet

**Cerebral Palsy**
- Chronic Neural Inflammation
- Exaggerated Sedentary Behavior
- Abnormal Musculoskeletal Development
- Muscle Spasticity

**Aging**
- Diminished Aerobic Capacity
- Sarcopenia
- Weakness
- Functional Deficit
- Fatigability

**Impaired Myogenesis**
- Decreased Mitochondrial Density
- Muscular Fibrosis

**Impaired Insulin Signaling**
- Incomplete beta-oxidation
- Altered Nutrient Partitioning

**Cytotoxic Oxidative Stress**
- Dyslipidemia

**Cardiovascular disease and type 2 diabetes**

**Physical & Cognitive Frailty**
- Diminished Aerobic Capacity

**Oxidative Stress**
- Hypertension
- Metabolic Inflexibility
- Hyperglycemia
- Impaired Insulin Signaling

**Muscle Pathology and Accelerated Functional Decline**
Greater Adipose Tissue Distribution and Diminished Spinal Musculoskeletal Density in Adults With Cerebral Palsy

Mark D. Peterson, PhD, MS, Peng Zhang, PhD, Heidi J. Haapala, MD, Stewart C. Wang, MD, PhD, Edward A. Hurvitz, MD

From the Department of Physical Medicine and Rehabilitation; Department of Surgery; and Morphomic Analysis Group, University of Michigan, Ann Arbor, MI.

Abstract

Objectives: To examine differences in adipose tissue distribution, lumbar vertebral bone mineral density (BMD), and muscle attenuation in adults with and without cerebral palsy (CP), and to determine the associations between morphologic characteristics.

Design: Cross-sectional, retrospective analyses of archived computed tomography scans.

Setting: Clinical treatment and rehabilitation center.

Participants: Adults (N=352) with CP (age, 38.8±14.4y; body mass, 61.3±17.1kg; Gross Motor Function Classification System levels, I–V) and a matched cohort of neurotypical adults. Of the 41 adults with CP included in the study, 10 were not matchable because of low body masses.

Interventions: Not applicable.

Main Outcome Measures: Computed tomography scans were assessed for visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) areas, psoas major area and attenuation in Hounsfield units (Hu), and cortical and trabecular BMDs.

Results: Adults with CP had lower cortical (β=−63.41 Hu, P<.001) and trabecular (β=−42.24 Hu, P<.001) BMDs and psoas major areas (β=−374.51mm², P<.001) and attenuation (β=−9.21 Hu, P<.001) after controlling for age, sex, and body mass. Adults with CP had greater VAT (β=3914.81mm², P<.001) and SAT (β=4615.68mm², P<.001). Muscle attenuation was significantly correlated with trabecular (r=.51, P=.002) and cortical (r=.46, P<.01) BMD, whereas VAT was negatively associated with cortical BMD (β=−.037 Hu/cm², R²=.13, P=.03).

Conclusions: Adults with CP had lower BMDs, smaller psoas major area, greater intermuscular adipose tissue, and greater trunk adiposity than neurotypical adults. VAT and cortical BMD were inversely associated.

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Muscle Attenuation

- Adults with CP had significantly less psoas muscle cross-sectional area ($\beta = -374.51 \text{ mm}^2$, $p < 0.001$)
- And lower muscle attenuation coefficient ($\beta = -9.27$, $p < 0.001$) in HU (i.e., lower muscle density)
Correlation between Psoas density and BMD at L4

- Adults with CP had significantly greater VAT ($\beta=3914.81 \text{ mm}^2$, $p<0.001$) and SAT ($\beta=4615.68 \text{ mm}^2$, $p<0.001$) depots.
- Muscle attenuation was significantly correlated with trabecular ($r=0.51$, $p=0.002$) and cortical ($r=0.46$, $p=0.006$) BMD.
- Whereas VAT was negatively associated with cortical BMD ($\beta=-0.037 \text{ HU/cm}^2$; $p=0.03$).
- N = 42 adults with CP
- Ages 18-50
- Compared to a age- and sex-matched reference population of adults (n~4,000)
- Percentiles presented range from 24<sup>th</sup> - 40<sup>th</sup>
• 38% had a past history of fragility fracture; 43% had a Z-score of ≤2.0 at the lumbar spine and 41% at the femoral neck.

• Hypogonadism was present in >20% of patients, was associated with reduced lean tissue mass, and reduced lumbar spine BMD.

• Reduced skeletal muscle mass index in 50% of males and nearly 80% of females.*

*SMI: appendicular lean mass divided by height$^2$ of 7.26 kg/m$^2$ in men and 5.5 kg/m$^2$ in women.
Critical Clinical Question

- Given the documented loss/absence of lean body mass (muscle and bone), and increased storage of visceral and muscular adipose tissue, is there an increased risk for chronic diseases in CP?

Prevalence of Various Chronic Diseases in CP

<table>
<thead>
<tr>
<th>Condition</th>
<th>Typically Developed</th>
<th>Cerebral Palsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>6.3%</td>
<td>9.2%</td>
</tr>
<tr>
<td>Asthma</td>
<td>9.4%</td>
<td>20.7%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22.1%</td>
<td>30.0%</td>
</tr>
<tr>
<td>Other Heart</td>
<td>9.1%</td>
<td>15.1%</td>
</tr>
<tr>
<td>Problems</td>
<td>2.3%</td>
<td>4.6%</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.4%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Emphysema</td>
<td>28.0%</td>
<td>43.6%</td>
</tr>
<tr>
<td>Joint Pain</td>
<td>17.4%</td>
<td>31.4%</td>
</tr>
<tr>
<td>Arthritis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Other Significant Covariates

Additionally:

- Age (OR: 1.05-1.07)
- **Obesity (OR: 1.07-4.37)**
- Degree of physical disability (OR: 1.49-4.21)
- **Physical inactivity (OR: 1.02-1.25)**

Were each independently associated with greater odds of the 8 chronic diseases
Multimorbidity in CP

- 435 individuals aged 40-60 years old, seen in clinic from 2011-2016, and with a CP Diagnosis Code.

- **Chronic conditions**: osteopenia/osteoporosis, myocardial infarction, stroke, coronary artery disease, impaired glucose tolerance/type 2 diabetes, other cardiovascular conditions, rheumatoid arthritis, osteoarthritis, asthma, emphysema, prehypertension/hypertension, and hyperlipidemia.

- **Multimorbidity**: ≥2 chronic conditions
**Multimorbidity in CP**

<table>
<thead>
<tr>
<th></th>
<th>GMFCS I-III</th>
<th>GMFCS IV-V</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-Obese</strong></td>
<td>53.6%</td>
<td>64.2%</td>
</tr>
<tr>
<td><strong>Obese</strong></td>
<td>75.8%</td>
<td>79.0%</td>
</tr>
</tbody>
</table>

Multimorbidity in CP

- You should be asking yourself, “but what about those individuals who’s BMI is below 30 but have excess fat stores...?”

<table>
<thead>
<tr>
<th>Model Predictor(s)</th>
<th>Estimate*</th>
<th>SE</th>
<th>Odds Ratio</th>
<th>95% CL</th>
<th>Pr &gt; ChiSq</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multimorbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (Reference: Males)</td>
<td>0.20</td>
<td>0.23</td>
<td>1.22</td>
<td>0.77-1.92</td>
<td>0.40</td>
</tr>
<tr>
<td>Age</td>
<td>0.05</td>
<td>0.02</td>
<td>1.05</td>
<td>1.01-1.09</td>
<td>0.02</td>
</tr>
<tr>
<td>Smoking Status (Reference: Non-Smoker)</td>
<td>1.18</td>
<td>0.43</td>
<td>3.26</td>
<td>1.42-7.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Obesity Status (Reference: Not Obese)</td>
<td>0.78</td>
<td>0.28</td>
<td>2.17</td>
<td>1.24-3.79</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>GMFCS Category (Reference: GMFCSI-III)</td>
<td>0.28</td>
<td>0.09</td>
<td>1.33</td>
<td>1.12-1.57</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

\(^{a}\geq2\) chronic conditions

\(^{a}\) Multimorbidity
Still not satisfied...

• What remains to be determined are the age-related trajectories of cardiometabolic diseases among adults with CP.
Age-Related Trends in Cardiometabolic Disease among Adults with Cerebral Palsy

- The Optum Clinformatics™ Data Mart Database is a de-identified nationwide claims database of all beneficiaries from a single private payer: comprises all enrollees who had medical and pharmacy insurance coverage at any time between January 1, 2001, and December 31, 2014—a total of 58,800,802 unique patients.

- We obtained access to data for all adults with CP during the period from 2001 to 2014. Beneficiaries were included in the data set if they had an ICD-9-CM code for a CP.

- Adults with at least 3 years of continuous enrollment on a single plan from the index diagnosis of CP, were included in the final analyses (n=2,659).

- Examined longitudinal trends of incident diabetes, hypercholesterolemia, hypertension, cardiac dysrhythmias, and atherosclerosis, by age categories: 18-39.9; 40-59.9; and ≥60 years.
Cumulative Incidence

• The CI of each of the cardiometabolic diseases in all enrollees ranged from 6.0% to 34.4% at 3+ years, and was:
  – 11.6% for diabetes mellitus
  – 34.4% for hypercholesterolemia
  – 28.9% for hypertension
  – 13.2% for cardiac dysrhythmias
  – and 6.0% for atherosclerosis.

• 3+ year CIs for hypercholesterolemia and hypertension are similar to the lifetime risk of these outcomes in the otherwise health, non-CP general population.
Diabetes

**Product-Limit Survival Estimates**

With Number of Subjects at Risk

Logrank p < 0.0001

**Follow-up Time (Days)**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>18 - 29</th>
<th>30 - 49</th>
<th>&gt;= 50</th>
</tr>
</thead>
</table>

[Graph showing survival probabilities over follow-up time with different age groups indicated.]
Hypertension

Product-Limit Survival Estimates
With Number of Subjects at Risk

Logrank p < .0001

Follow-up Time (Days)

Age Group
- Blue: 18 - 29
- Red: 30 - 49
- Green: >= 50
Hypercholesterolemia

Product-Limit Survival Estimates
With Number of Subjects at Risk

Logrank p < .0001

Survival Probability

Follow-up Time (Days)

Age Group
- 18 - 29
- 30 - 49
- >= 50
Cardiac Dysrhythmias

Product-Limit Survival Estimates
With Number of Subjects at Risk

Follow-up Time (Days)

Survival Probability

Age Group
18 - 29
30 - 49
>= 50

Logrank p < .0001
Atherosclerosis

Product-Limit Survival Estimates
With Number of Subjects at Risk

Survival Probability

Follow-up Time (Days)

Age Group  
18 - 29  
30 - 49  
>= 50

Logrank p < .0001
• Fully-adjusted multivariable survival analyses demonstrated a significant effect of higher HRs in middle age (HR 1.40-2.72; all p<0.05) and older adults (HR 2.19-5.94; all p<0.05) as compared to young adults.

In Review
CP and other “rehab” populations are severely understudied from the context of Frailty and Sarcopenia Research.

We are also interested in implications for healthcare utilization at the population level.
<table>
<thead>
<tr>
<th>Measures</th>
<th>Normal weight</th>
<th>Overweight</th>
<th>Differences</th>
<th>Obese</th>
<th>Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals with physical disabilities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total healthcare costs ($)</td>
<td>8,341.19*</td>
<td>8,571.34*</td>
<td>-230.15</td>
<td>9,448.21***</td>
<td>-1,107.02**</td>
</tr>
<tr>
<td>Any office visits</td>
<td>0.83***</td>
<td>0.85***</td>
<td>-0.02**</td>
<td>0.87***</td>
<td>-0.04**</td>
</tr>
<tr>
<td>Any hospitalization</td>
<td>0.12***</td>
<td>0.12***</td>
<td>0.00</td>
<td>0.13***</td>
<td>-0.01**</td>
</tr>
<tr>
<td>Number of office visits</td>
<td>10.77***</td>
<td>11.13***</td>
<td>-0.36**</td>
<td>11.75***</td>
<td>-0.98**</td>
</tr>
<tr>
<td>Number of nights hospitalized</td>
<td>7.47***</td>
<td>7.16***</td>
<td>0.31</td>
<td>6.88***</td>
<td>0.59</td>
</tr>
<tr>
<td>Individuals without physical disabilities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total healthcare costs ($)</td>
<td>4,251.62*</td>
<td>4,368.93*</td>
<td>-117.31</td>
<td>4,815.88*</td>
<td>-564.26**</td>
</tr>
<tr>
<td>Any office visits</td>
<td>0.70*</td>
<td>0.72*</td>
<td>-0.02**</td>
<td>0.75*</td>
<td>-0.05**</td>
</tr>
<tr>
<td>Any hospitalization</td>
<td>0.07*</td>
<td>0.07*</td>
<td>0.00</td>
<td>0.08*</td>
<td>-0.01**</td>
</tr>
<tr>
<td>Number of office visits</td>
<td>6.64*</td>
<td>6.86*</td>
<td>-0.22**</td>
<td>7.25*</td>
<td>-0.61**</td>
</tr>
<tr>
<td>Number of nights hospitalized</td>
<td>5.14*</td>
<td>4.93*</td>
<td>0.21</td>
<td>4.73*</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Interestingly...

- Costs associated with PDs were >95% higher than non-physically disabled adults, regardless of BMI.
- Healthcare utilization from adults with PDs + obesity represents ~50% of the total annual medical costs attributed to obesity in the U.S.
- A staggering finding considering that this subset of individuals corresponds to approximately 7% of the total population.
- WHY???
Individuals with Physical Disabilities

Individuals without Physical Disabilities

Ages 18 to 44

Ages 45 to 64

Ages 65 and over

Source: Data are from the household component files of the 2002-2011 Medical Expenditure Panel Survey.

Normal Weight | Overweight | Obese
Global Model of Aging, Weakness, and Disability

Muscle mass and strength vs Age

- Early life
- Adult life
- Older life

Range in individuals

Disability threshold
Thank you!

- Email: mdpeterz@med.umich.edu and ehurvitz@med.umich.edu