Secondary Muscle Pathology and Metabolic Dysregulation in Adults with Cerebral Palsy

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Cerebral Palsy as a Model

- **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)**

*Paneth et al. *Clinical Perinatology*. 33: 2006.

Function

- Functional status as child predicts adulthood
- Decline is frequently, but not always seen
- Decline may relate to secondary factors

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Related to Early Status (Day, 2004)

- **Walk and stairs at 10→ 23% decline**
- **Some walking, no w/c→ some decline, some improvement**
- **W/C use→generally declined**
- **After 25 years old, little improvement, some decline**
- **Age 60-75, significant decline in ambulation, less so in speech and self feed**

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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

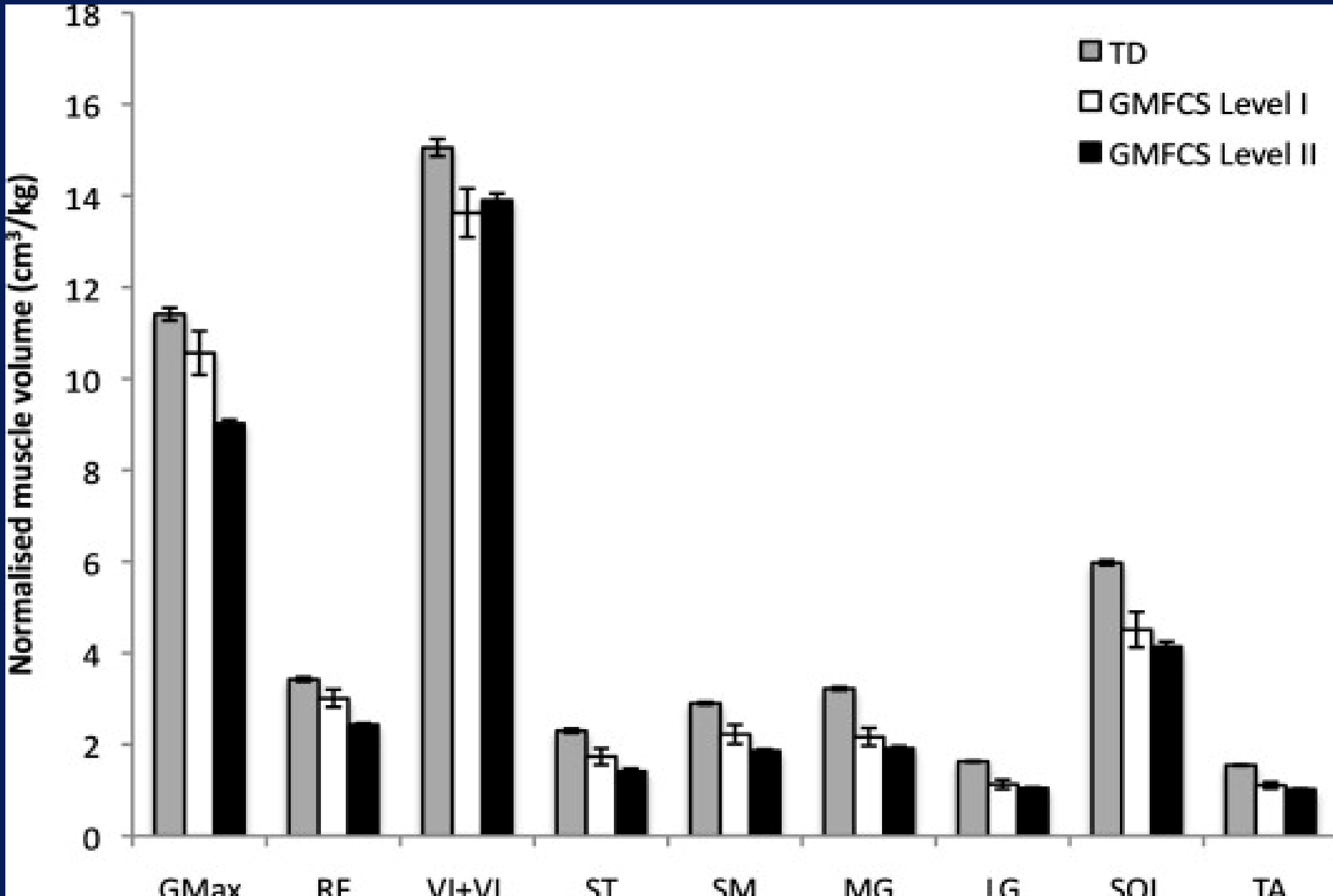
Contributing Factors

- **Pain and Fatigue**
- **Musculoskeletal problems (contractures, dislocations)**
- **Inadequate attention to function (no therapies)**
- Accessibility—Inadequate access to care
- Poor levels of fitness

Fitness in Children & Adults with CP

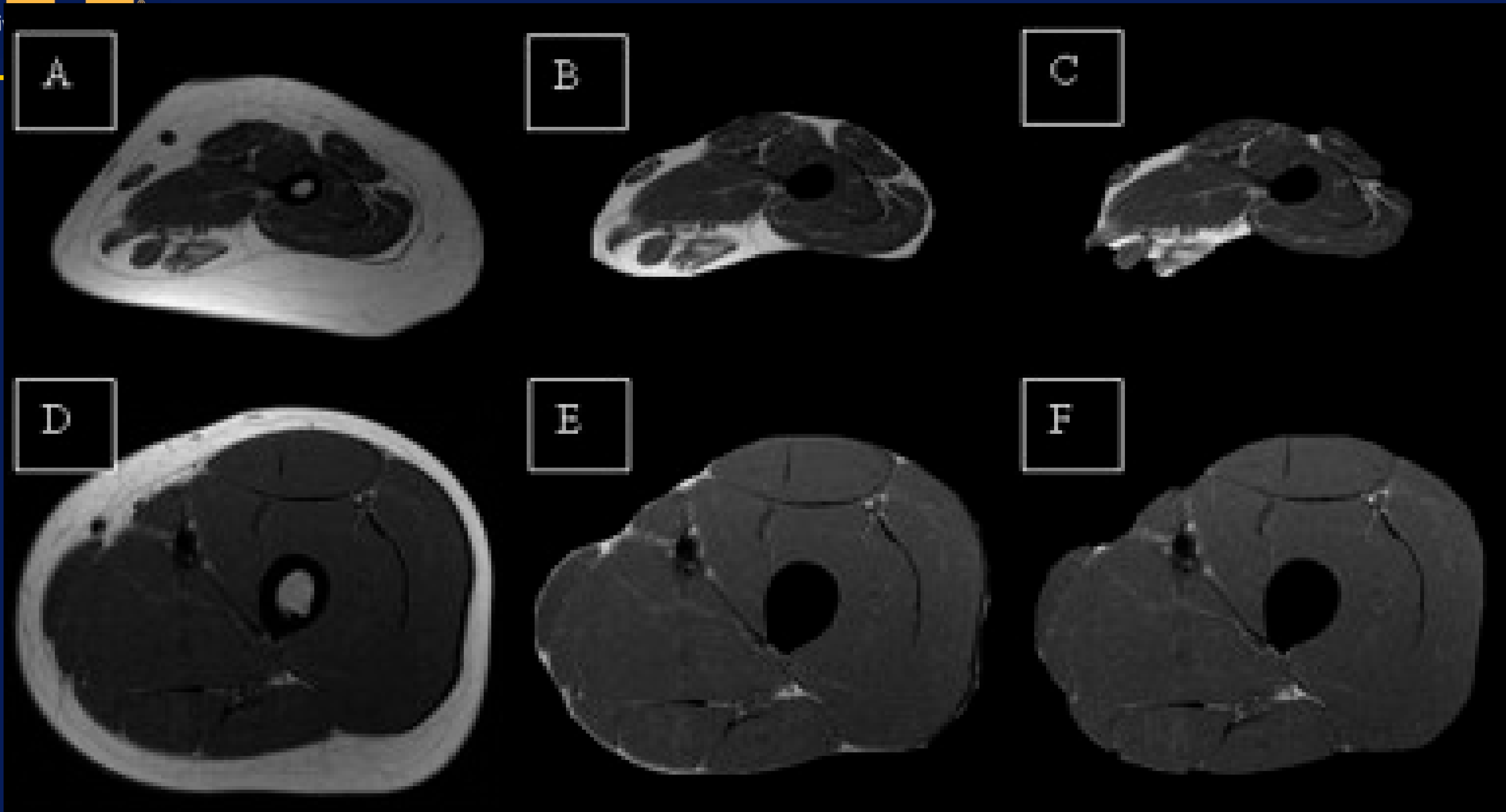
- **Decreased aerobic capacity**
- **Decreased strength**
- **Decreased flexibility**
- **Decreased levels of Physical Activity**
  - Especially health-related PA
- **Cardiovascular disease significant cause of death**
  - Strauss 1999
- **Risk of overweight and obesity**

Muscle volume in CP



Noble et al., *Brain Develop*, 2014 , 36(4): 294–300

Not only about age.



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.

Inter- and Intramuscular Fat in CP

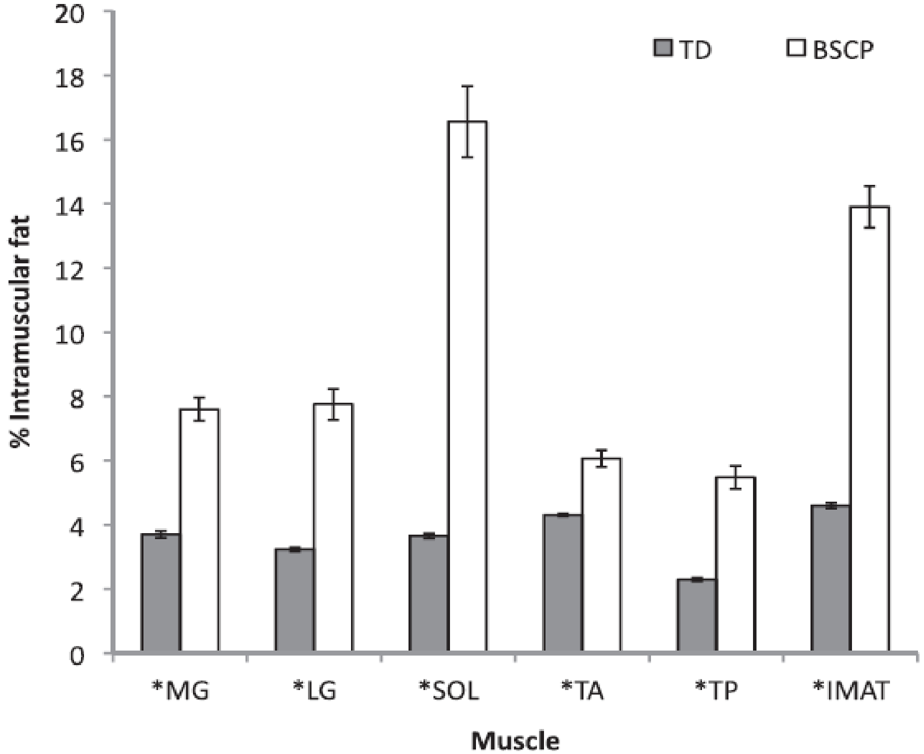


Figure 2 Percentage IntraMF and IMAT in the medial gastrocnemius (MG), lateral gastrocnemius (LG), soleus (SOL), tibialis anterior (TA), tibialis posterior (TP) and in the BSCP group (white) and TD group (grey). IMAT and IntraMF in all muscles were significantly different between groups ($p < 0.05$). Error bars represent the standard error of each group.

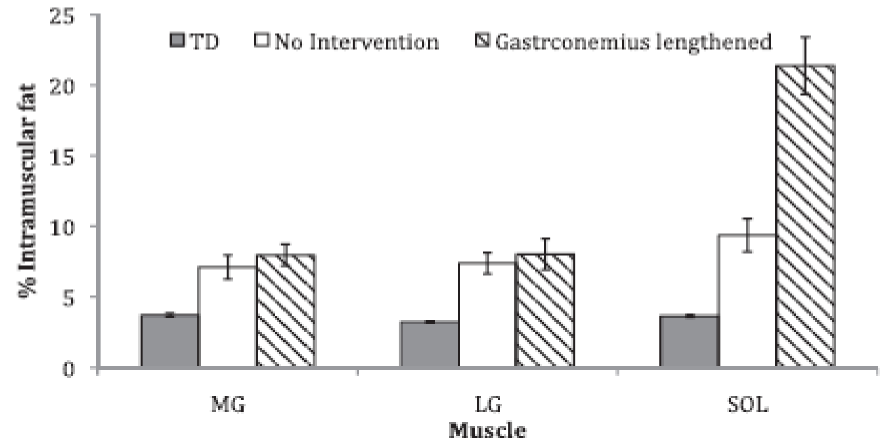
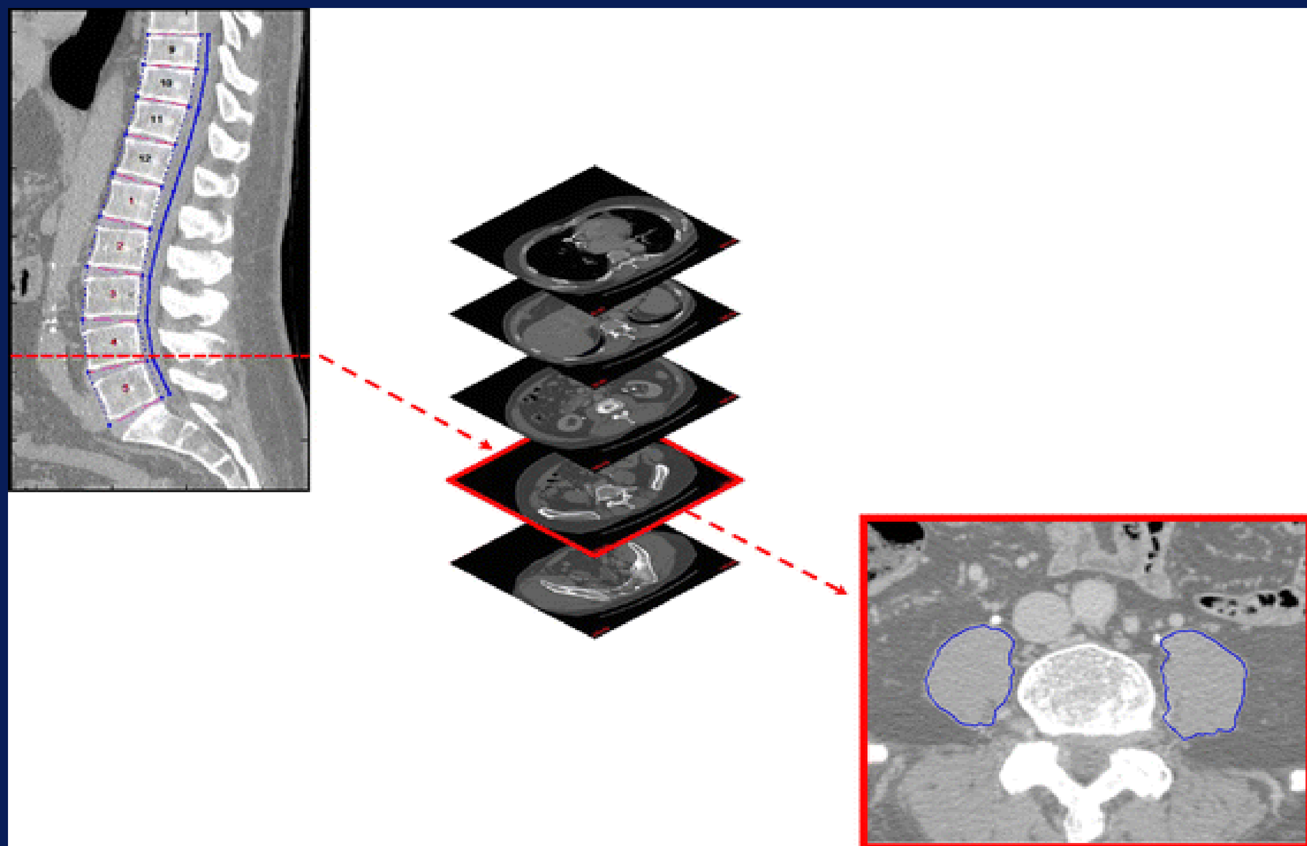


Figure 5 Percentage intramuscular fat in the medial gastrocnemius (MG), lateral gastrocnemius (LG) and soleus (SOL) for the TD group (grey), the no intervention BSCP subjects (white) and the gastrocnemius recession BSCP subjects (striped).

Noble et al., *BMC Musc Disor*, 2014, 15:236

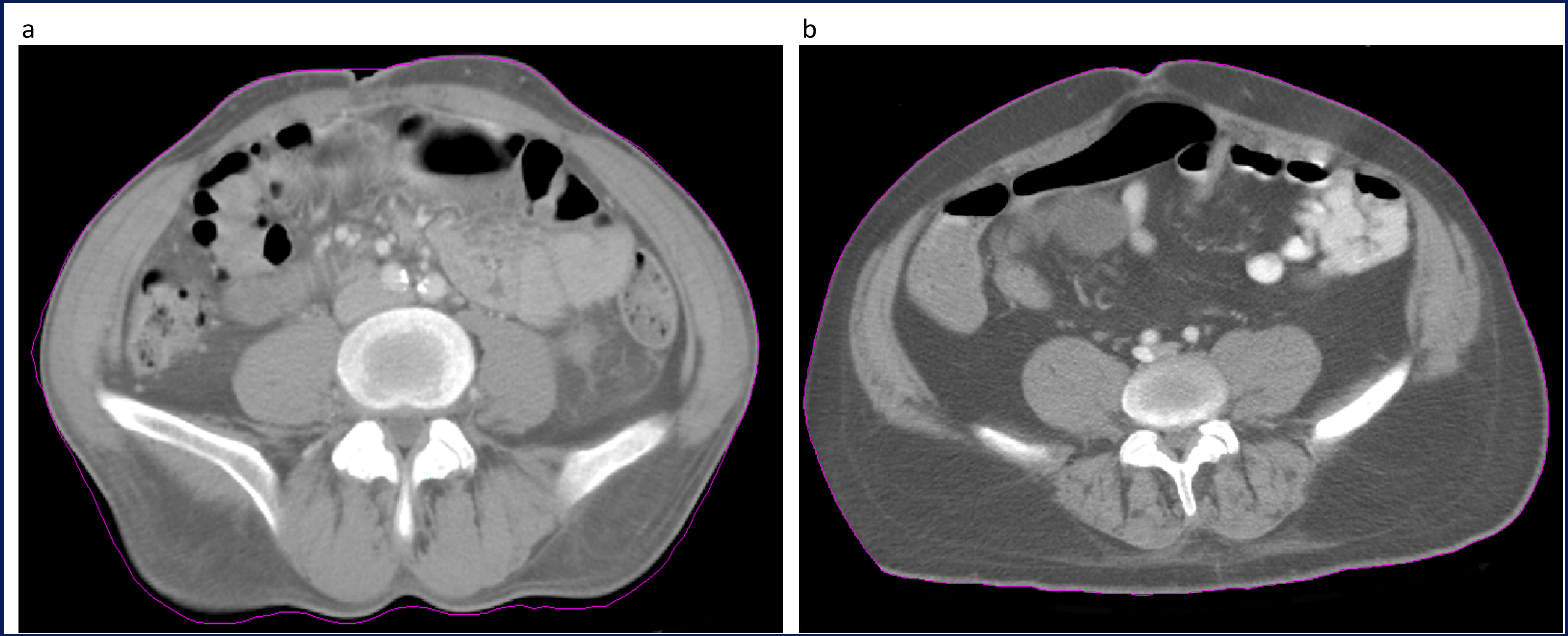
Analytic Morphomics in CP

CT scans were processed and analyzed for visceral fascial determination, and to draw contours of psoas major muscles at the L4 level



Peterson, Hurvitz, et al, *Arch Phys Med Rhehab.* In Review

Example control/case



(a) a 53 year old, typically-developed male (65 kg body mass), and (b) a 54 year old male with CP (66 kg body mass).

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Results

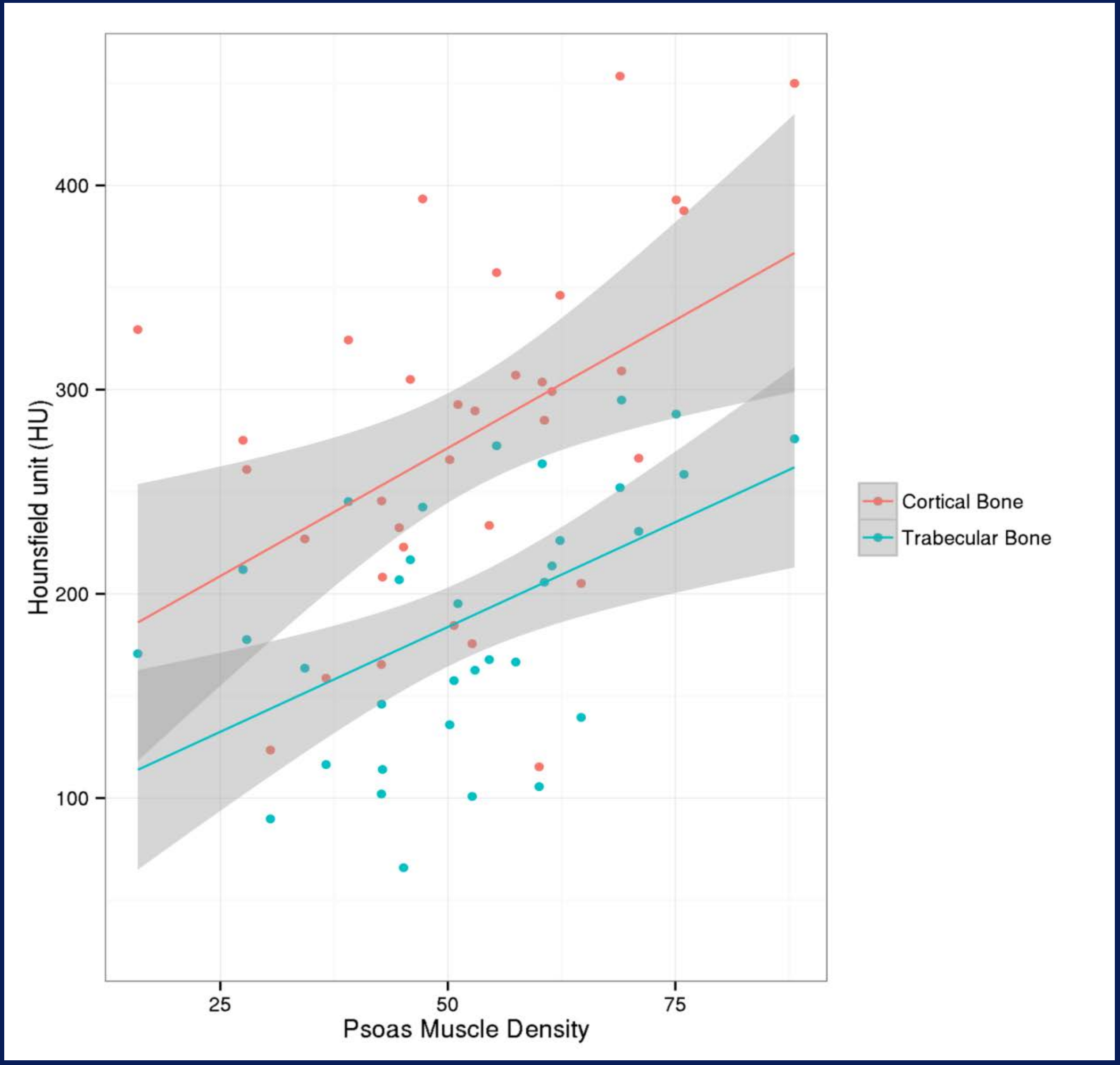
<u>After controlling for age, sex, and body mass, adults with CP had</u>

- **Lower cortical BMD (β=-63.41 HU, $p<0.001$)**
- **Lower trabecular BMD (β=-42.24 HU, $p<0.001$)**
- **Smaller psoas major areas (β=-374.51 mm^2, $p<0.001$)**
- **Lower attenuation (β=-9.21 HU, $p<0.001$)**
- **Greater VAT areas (β=3914.81 mm^2, $p<0.001$)**
- **Greater SAT areas (β=4615.68 mm^2, $p<0.001$)**

Correlation between Psoas density and BMD at L4

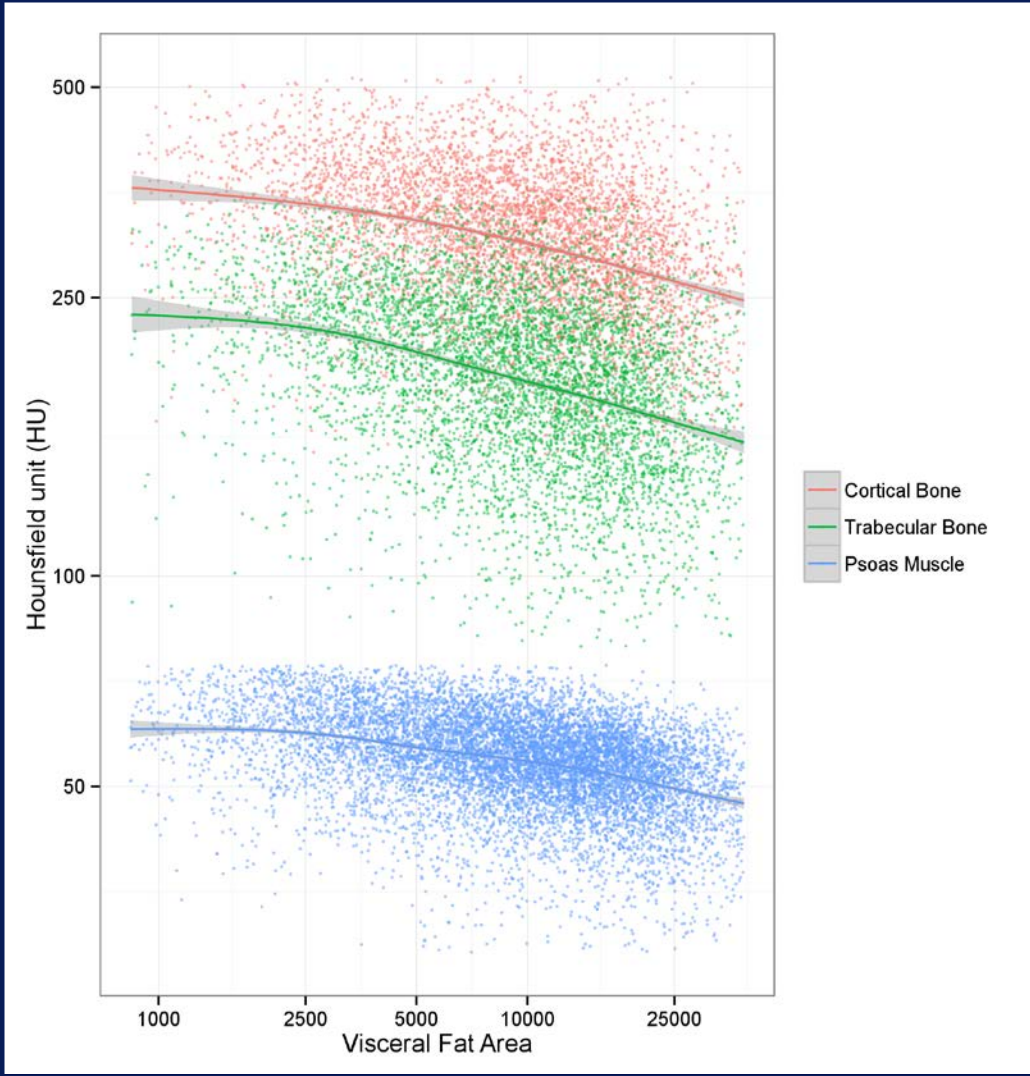
- Muscle attenuation was significantly correlated with trabecular (r=0.51, p=0.002) and cortical (r=0.46, p=0.006) BMD;

- Whereas VAT was negatively associated with cortical BMD (β=-0.037 HU/cm^2; r^2=0.13; p=0.03).



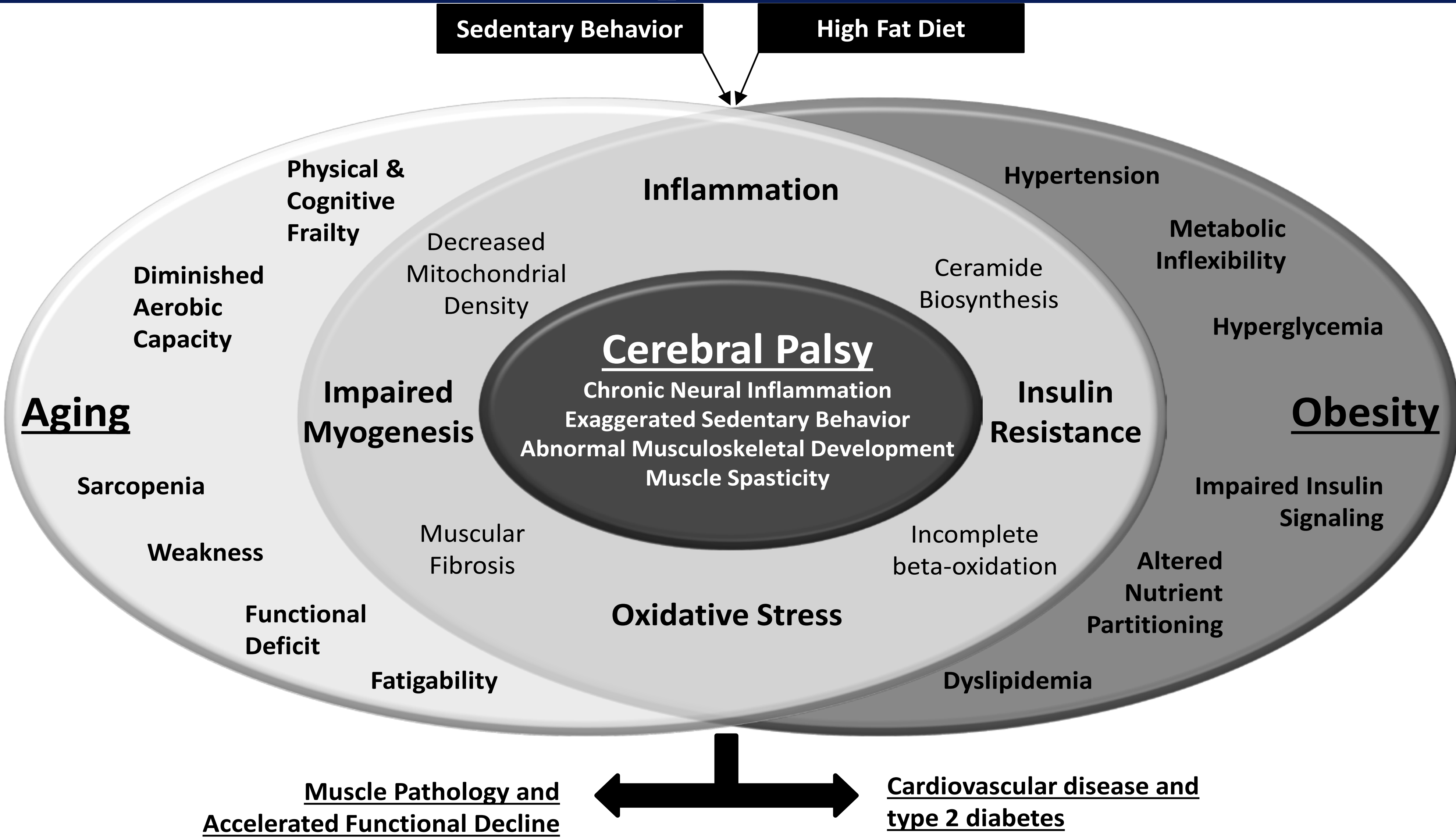
Importantly, this is not specific to CP

- **N=4200**
- **Densities of muscles and bones were robustly and inversely associated with visceral adiposity**
- **Somewhat contrary to the widely-held belief about BMD and obesity**



Zhang, P, Peterson, M, et al. *Am J Clin Nutr.* 101(2): 337-343. 2015.

Not so Novel a Concept, but…



Peterson MD, Hurvitz, E. et. al.. *AJP-Endo Metab.* 2012 303(9):E1085-93.

Central Adiposity as a Risk Factor in CP

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ORIGINAL ARTICLE

Predictors of Cardiometabolic Risk Among Adults With Cerebral Palsy

Mark D. Peterson, PhD, Heidi J. Haapala, MD, Edward A. Hurvitz, MD

ABSTRACT. Peterson MD, Haapala HJ, Hurvitz EA. Predictors of cardiometabolic risk among adults with cerebral palsy. Arch Phys Med Rehabil 2012;93:816-21.

Objective: To examine the independent association between various anthropometric indicators and standard clinical markers of cardiometabolic health risk among adults with cerebral palsy (CP).

Design: Cross-sectional study.

Setting: Clinical center for CP treatment and rehabilitation.

Participants: Adults with CP (N=43) with a mean age ± SD of 37.3±13.2 years, and Gross Motor Function Classification System (GMFCS) levels of I−V.

Interventions: Not applicable.

Main Outcome Measures: Adults with CP were assessed for body mass index (BMI), waist circumference (WC), hip circumference (HC), waist-to-hip ratio (WHR), waist-to-height ratio (WtHR), and serum lipid profiles. Data were analyzed with multiple regression analysis and general linear models, and are reported as means ± SDs.

Results: Mean BMI was 29.1±7.8kg/m². BMI was not associated with any measures of cardiometabolic risk. Using GMFCS categories (2 groups: GMFCS levels I–III and IV–V), BMI was significantly lower among GMFCS levels IV–V (24.2±6.2kg/m²) versus GMFCS levels I–III (30.1±7.6kg/m²). WC and WtHR were not correlated with any cardiometabolic outcomes. Conversely, measures of WHR were independently associated with various indices of risk, including total cholesterol to high-density lipoprotein (HDL) cholesterol ratio (r=.45; P<.05), HDL cholesterol (r=−.51; P<.01), and triglycerides (r=.40; P<.05), suggesting that greater WHR was indicative of elevated risk.

Conclusions: It is likely that WHR represents a stronger predictor of risk, because this measure was robustly and independently associated with 3 primary clinical markers of cardiometabolic health in adults with CP.

Key Words: Anthropometry; Body mass index; Cerebral palsy; Hyperlipidemia; Obesity; Rehabilitation.

INDIVIDUALS WITH cerebral palsy (CP) have permanent neurologic impairment, which compromises motor function, mobility, and balance. In conjunction with reduced muscle volume,[1] these factors predispose adults with CP to inevitable and exaggerated latent health risks.[2] While the specific mechanisms of secondary chronic disease are not well defined, ample evidence exists to confirm that individuals with CP have lower fitness,[3,4] less muscle mass,[1] diminished bone density,[5,6] neuromuscular inefficiency,[2,7,8] and significantly reduced functional reserve throughout the span of adulthood. Along with the hallmark neuromuscular impairments and motor deficits, the decreased physical activity and aerobic fitness that occur among persons with CP have prompted an intuitive comparison model of disability with spinal cord injury[9]—a population with significant muscular atrophy, increased intramuscular adiposity, insulin resistance, hyperlipidemia, atherogenesis, and elevated prevalence of type II diabetes.[10,11] However, in contrast to the spinal cord injury model, individuals with CP have the added potential risk of diminished activity, increased adiposity, and obesity-related metabolic dysregulation from birth. Thus, there is an ongoing circular cause and consequence of events that leads toward a simultaneous loss of musculoskeletal morphology and physiology, as well as exaggerated risk for cardiometabolic health complications.

Because obesity is an independent risk factor for insulin resistance and atherogenesis, if left untreated this collection of pathophysiologic factors precipitates heightened risk for cardiometabolic disease and early all-cause mortality.[12,13] Most research pertaining to obesity among individuals with CP has been conducted to characterize prevalence[14,15] or to compare and cross-validate anthropometric and body composition strategies.[16,17] Several studies have identified a general increased prevalence of obesity among children with CP,[14,15] but this has yet to be well documented in adults.

While most studies have focused on measurement strategies for relative adiposity or the validation of methods to predict body fat stores among patients with CP,[17] findings also reveal significantly diminished body protein[18] and specific muscle tension[19] and thus highlight the implications of skeletal muscle deterioration. As a result, individuals with muscle atrophy and

List of Abbreviations

BMI	body mass index
CP	cerebral palsy
GMFCS	Gross Motor Function Classification System
HC	hip circumference
HDL-C	high-density lipoprotein cholesterol
LDL-C	low-density lipoprotein cholesterol
TChol	total cholesterol
TG	triglyceride
VAT	visceral adipose tissue
WC	waist circumference
WHR	waist-to-hip ratio
WtHR	waist-to-height ratio

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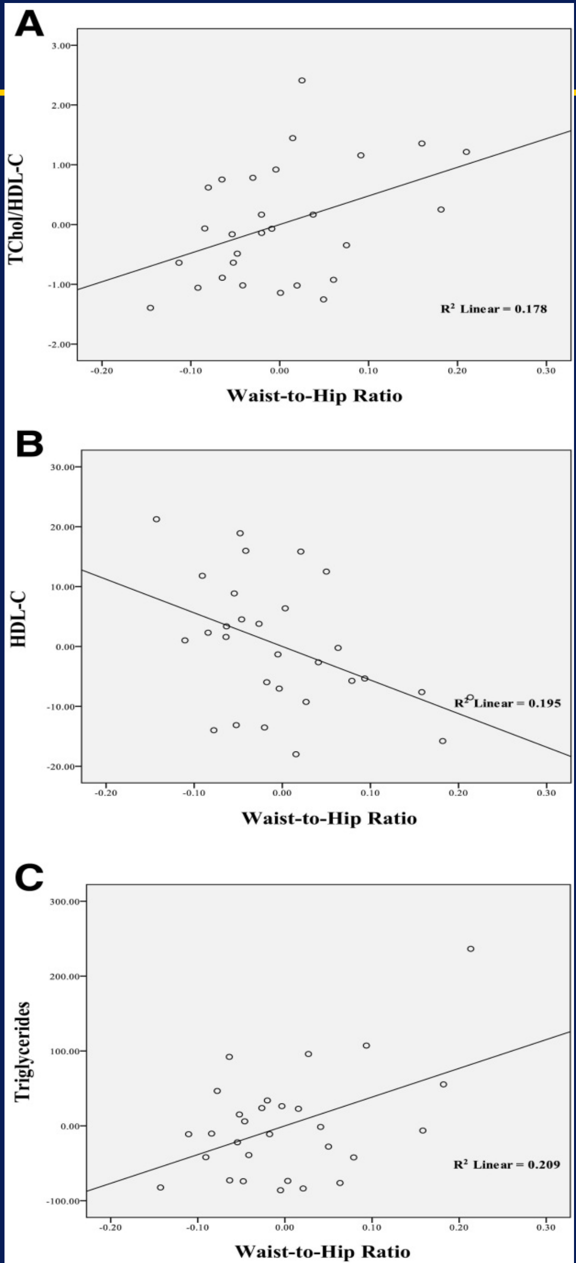
doi:10.1016/j.apmr.2011.12.024



Central Adiposity as a Risk Factor in CP

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Peterson *et al. Nutrition & Metabolism* 2014, **11**:22
http://www.nutritionandmetabolism.com/content/11/1/22

Nutrition&Metabolism

RESEARCH Open Access

Abdominal obesity is an independent predictor of serum 25-hydroxyvitamin D deficiency in adults with cerebral palsy

Mark D Peterson*, Heidi J Haapala, Ashish Chaddha and Edward A Hurvitz

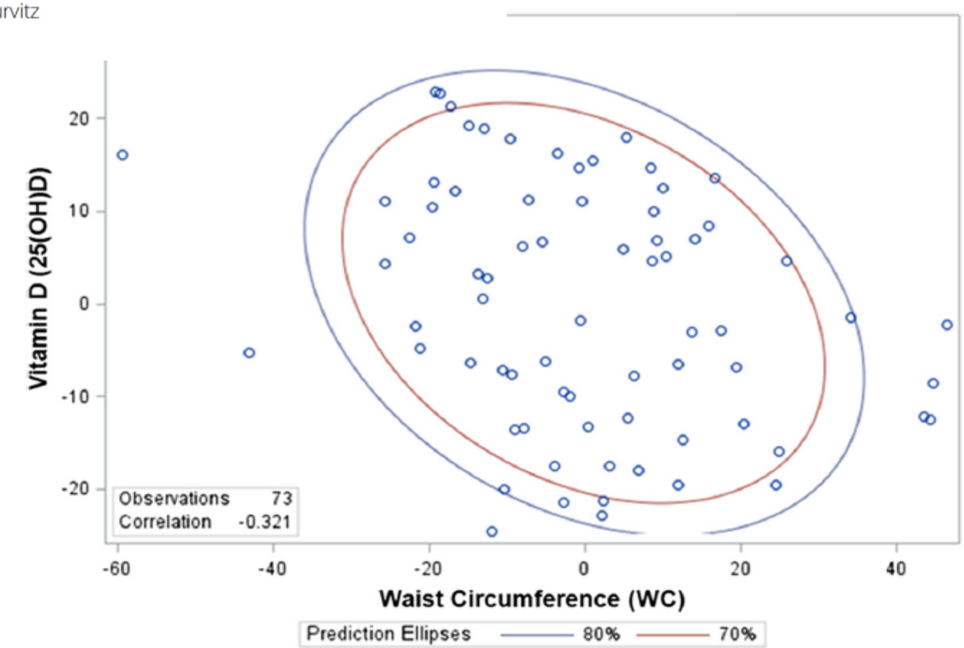
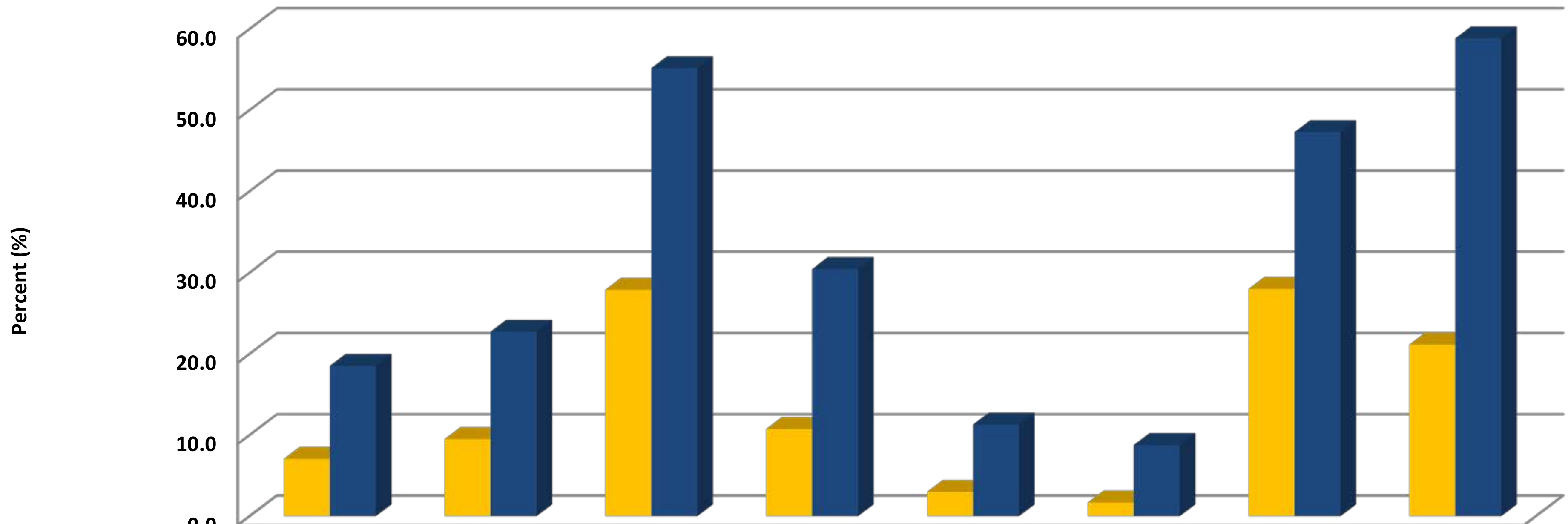


Figure 2 Partial residual scatter plot for the variables waist circumference (WC) and 25-hydroxyvitamin D after controlling for the effect of variables age, sex, and GMFCS (with 70% and 80% prediction ellipses).

N=1,036 Adults with CP

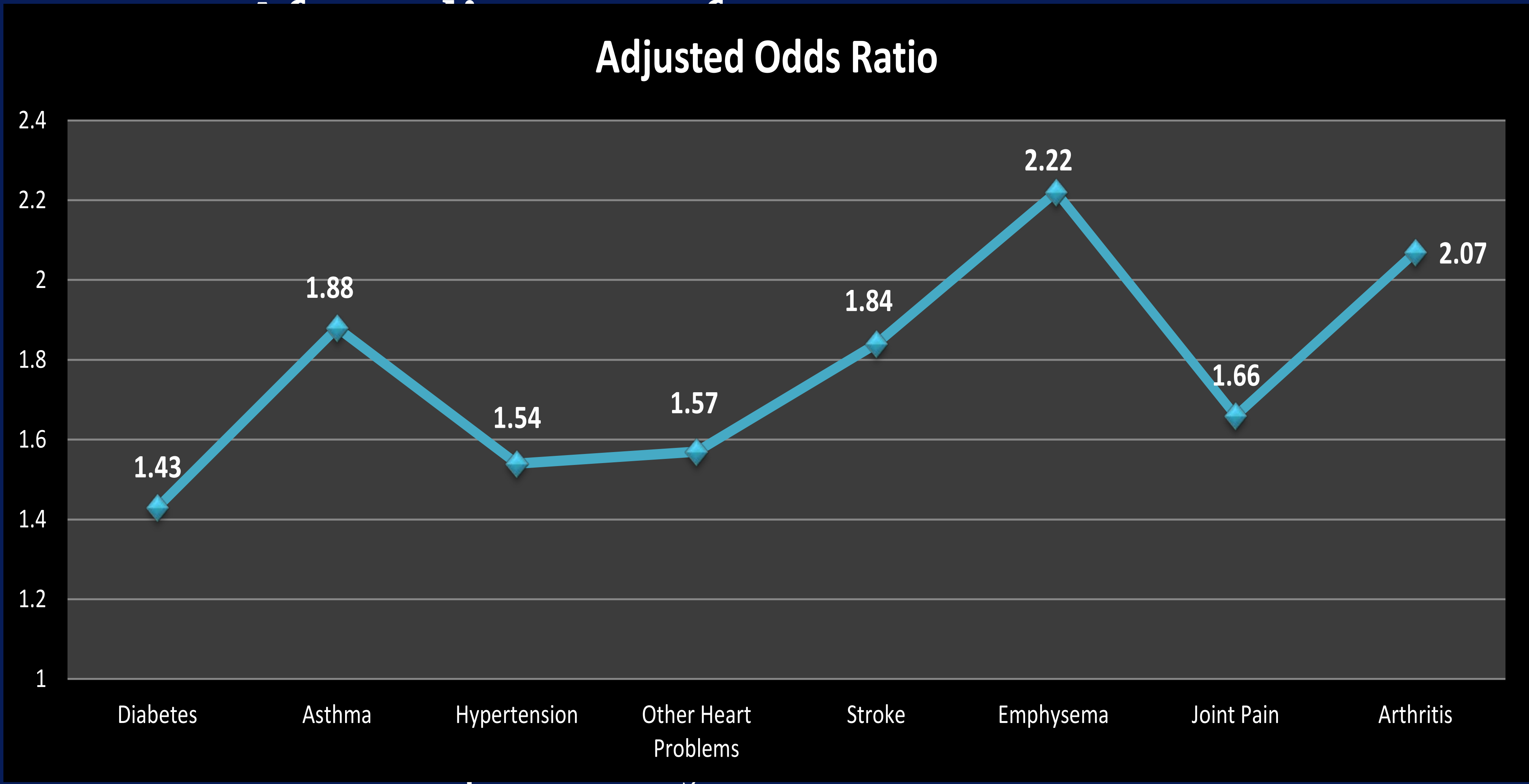
Prevalence of Various Chronic Diseases in CP



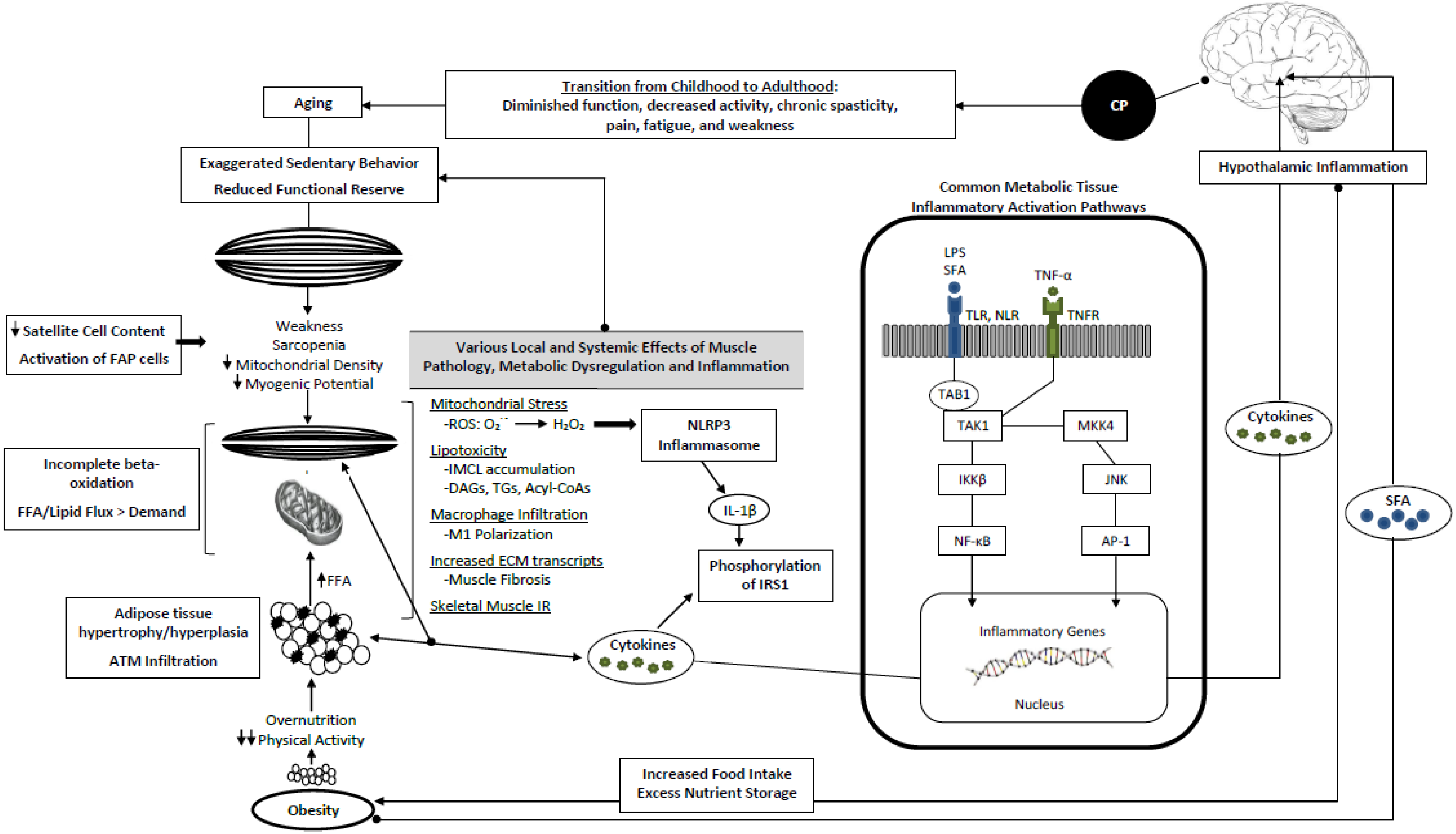
	Type 2 Diabetes	Asthma	Hypertension	Other Heart Problems	Stroke	Emphysema	Joint Pain	Arthritis
Typically Developed	7.1	9.5	27.9	10.7	3.0	1.7	28.0	21.1
Cerebral Palsy	18.5	22.7	55.2	30.4	11.3	8.8	47.3	58.8

Peterson, M, Ryan, J., Hurvitz, E. and Mahmoudi *In Review*.

Fully Adjusted Model



Conceptual Model of Mechanisms & Targets



Peterson MD, Hurvitz, E. et. al.. *AJP-Endo Metab.* 2012 303(9):E1085-93.

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Individuals with CP are predisposed to various secondary health complications that may be directly “caused” by modifiable lifestyle factors such as exaggerated sedentary lifestyles and insufficient physical activity

Nooijen C, et al. *Journal of rehabilitation medicine*. 2014. 25;46(7):642-7.

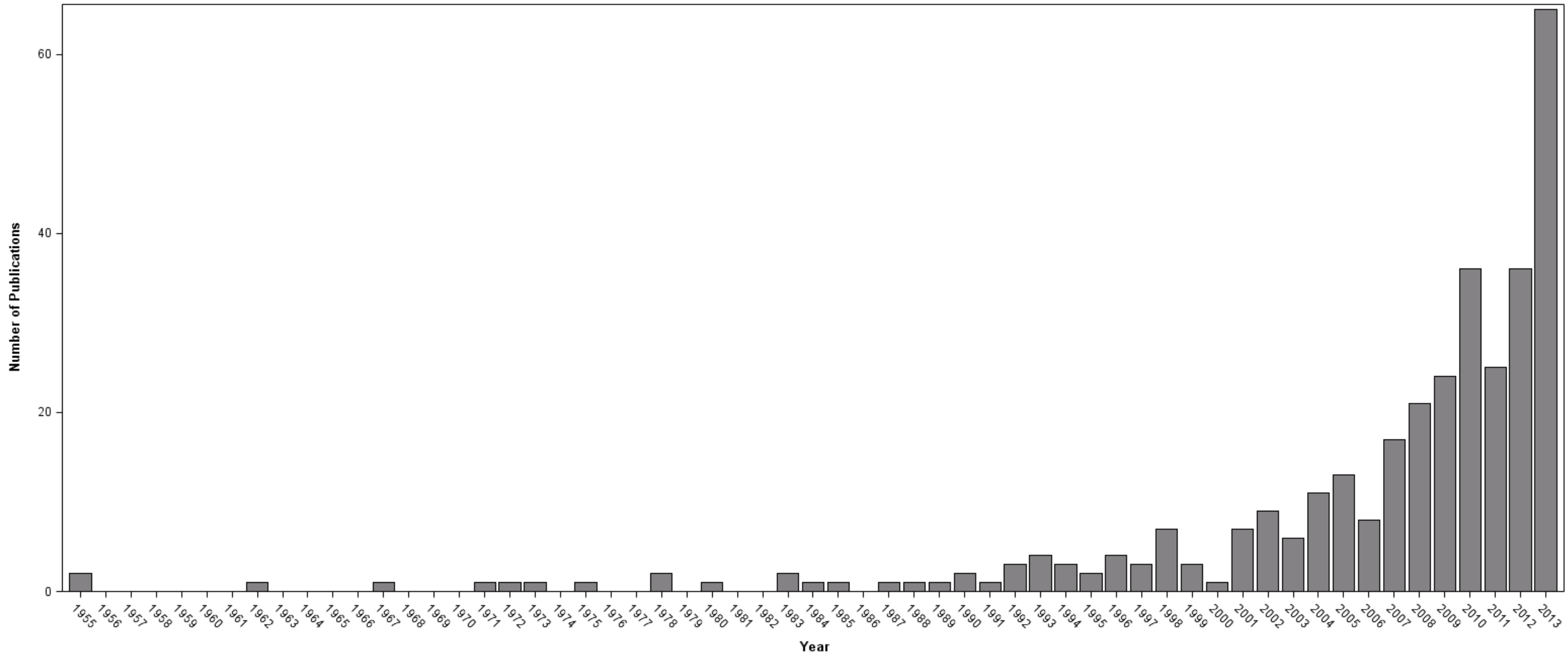
Nooijen C, et al. *Journal of neuroengineering and rehabilitation*. 2014;11:49

Rabani, et al. *Dev Med Child Neurol*. 2014; 56(7): 673–680

Ryan J, et al. *Physical Therapy*. 2014;94(8):1144-53

Maher CA, et. Al.. *Dev Med Child Neurol*. 2007;49:450-457

Publication trends for the topic of physical activity or exercise training in cerebral palsy: 1955-2014.



***As of June 2014, there were 39 publications meeting inclusion criteria. At approximately 6.5 publications per month, this is the highest rate per year (i.e., in 2013 there was an average of 5.4 per month).**

- **Fundamental movement skills are the primary predictor of activity participation among children with CP, with those who are more proficient tending to be more physically active**
  - Capio CM, et al. *Res Dev Disabil*. 2012;33:1235-1241

- **Habitual physical activity is directly associated with motor functional capacity, i.e., higher HPA levels associated with greater motor capacity.**
  - Keawutan et al., *Res Dev Disabil*. 2014; 35(6):1301–1309

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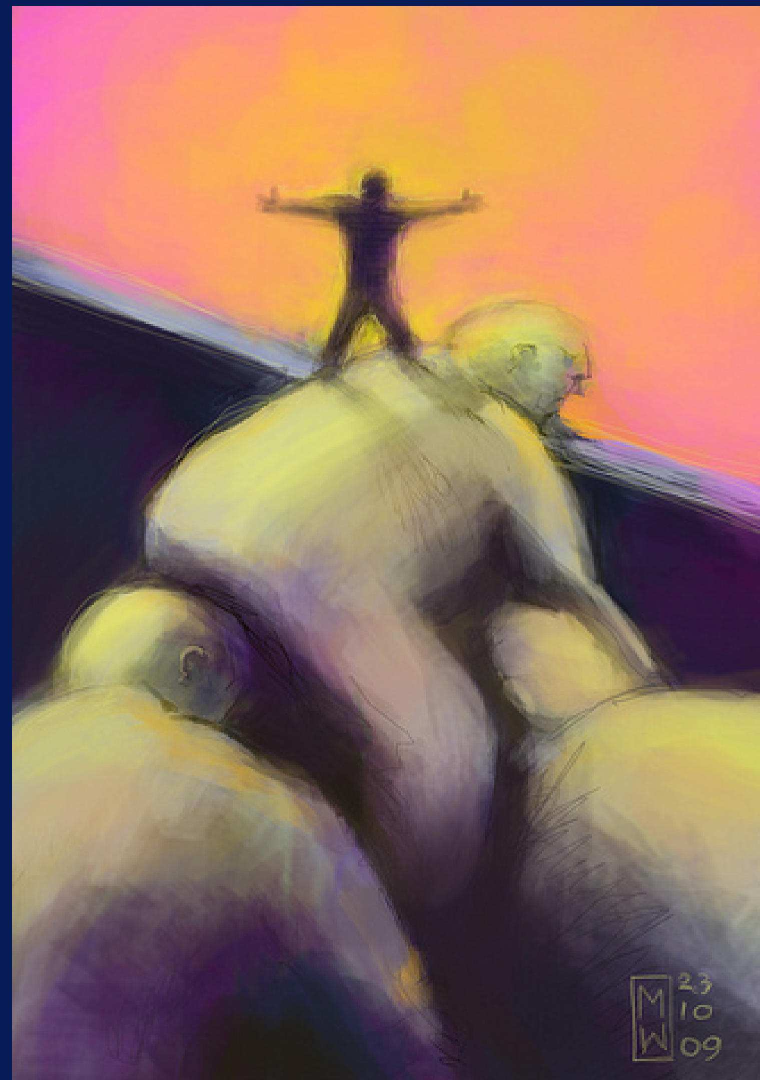
- Dr. James McClain (NIH)
- NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

CRRLD Center *for* Rehabilitation Research *using* Large Datasets



Thank you

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