Proving the Obvious: Next Steps for the Demystification of Ehlers Danlos Hypermobility Type

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Why don’t doctors know about EDS?

- In my medical school (1994-1998) there was one slide (in 4 years) that mentioned EDS
- In my genetics and pediatrics residency (1998-2003), the standard was “some patients get arthritis when they are older. . .”
- Education of providers is slow
  - Educational sources have to be accessible, credible, and acceptable.
  - There are other barriers . . .

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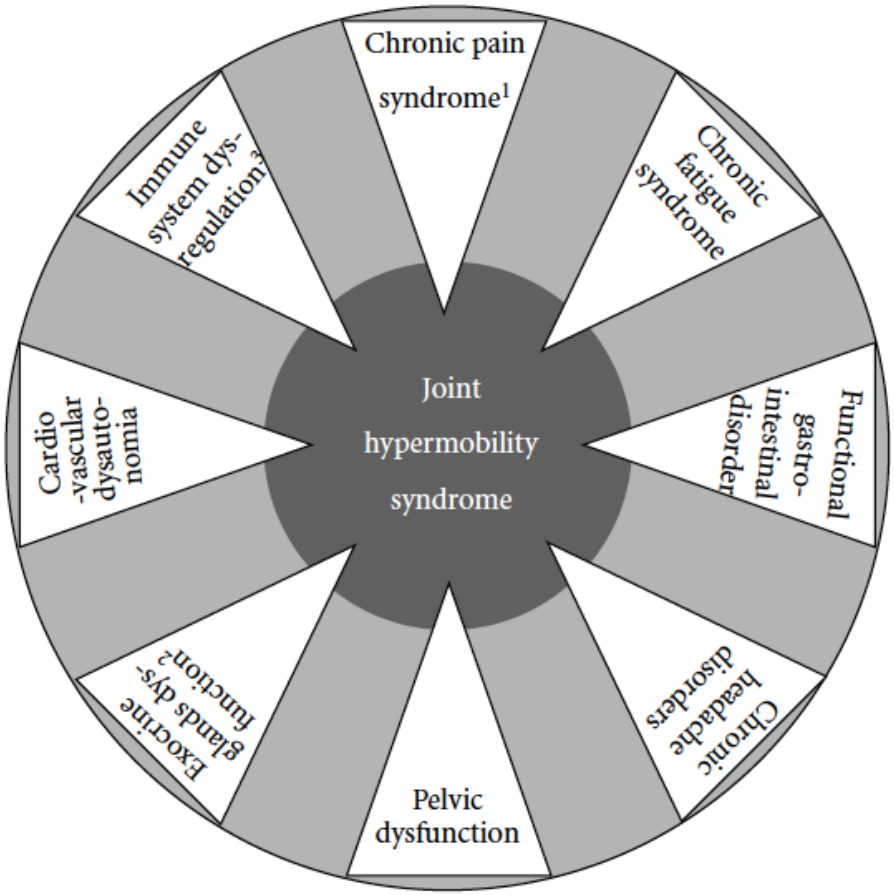
Current model of EDS-HT / JHS



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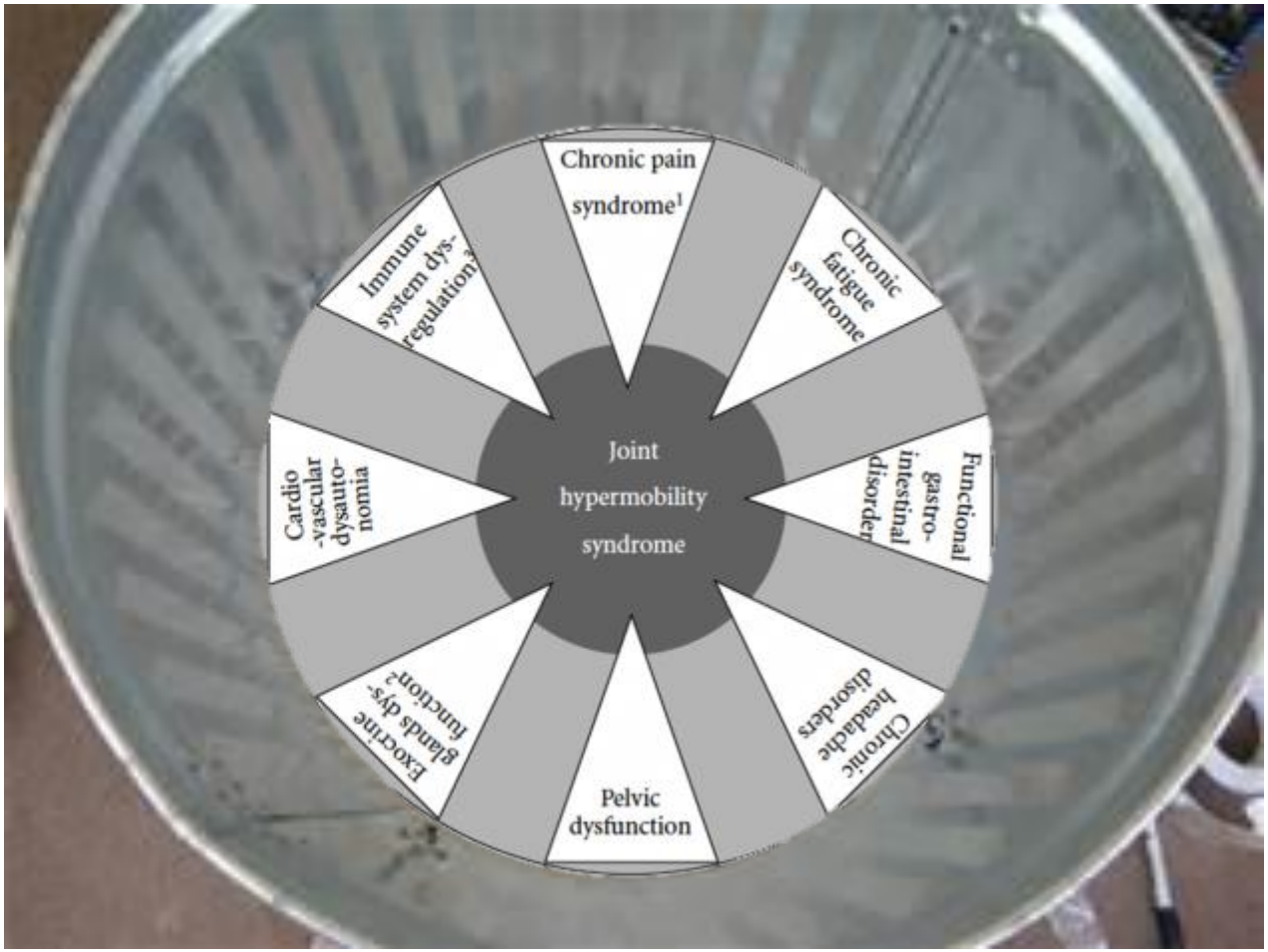
ISRN Dermatol. 2012;2012:751768. doi: 10.5402/2012/751768.

How providers see the disorder . . .



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What are the barriers to acceptance?

- Perception that it is a rare disorder
- Misunderstanding of diagnostic criteria
  - "You can't make a diagnosis without a gene test/biopsy"
  - "Your skin is not stretchy"
- Lack of pathophysiology
  - How does loose collagen translate into the phenotype?
  - Why are nerves affected (dysautonomia)?
  - Where does anxiety come in?

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How do we demystify the disorder?

- As providers, we see patterns among our patients
- Many of these patterns are “known” but remain un-investigated.
- Research must demonstrate that these patterns exist and *place them into a meaningful context*.
- No more trash cans!

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EDS is *NOT* a rare disorder

- Pattern recognition: We see far more EDS than would be expected

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How rare is rare?

- Current estimates vary widely
  - 1 in 10,000 to 1 in 15,000 (ednf.org 2010 MRG)
  - 0.5 - 2% of the population.
    - Based on “professional estimates” and extrapolation from estimates in fibromyalgia populations
- Study from Avon, U.K. evaluated pts. over time
  - Beighton score of ≥6, age 14. Rechecked at 17
  - Of 2901 asymptomatic, 4.7% were hypermobile
  - 9-16% developed joint problems / pain ~ 0.4 -0.7%
  - Arthritis Rheum. 2013 Apr;65(4):1107-15. doi: 10.1002/art.37836.

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How common is EDS-HT?

- Bioinformatic search at Cincinnati Children's
  - Patients with hypermobility diagnosis between ages 5 and 18: 2,794
  - Total patients of same ages: 526,371
  - Estimate at CCHMC: ~0.5%, or 1/200
- Connective Tissue Clinic Data
  - Over the past 2½ years, we have evaluated 2218 new patient visits (including adults), ~95% of whom are diagnosed with EDS-HT.
  - 7-10% of the entire U.S. EDS population?

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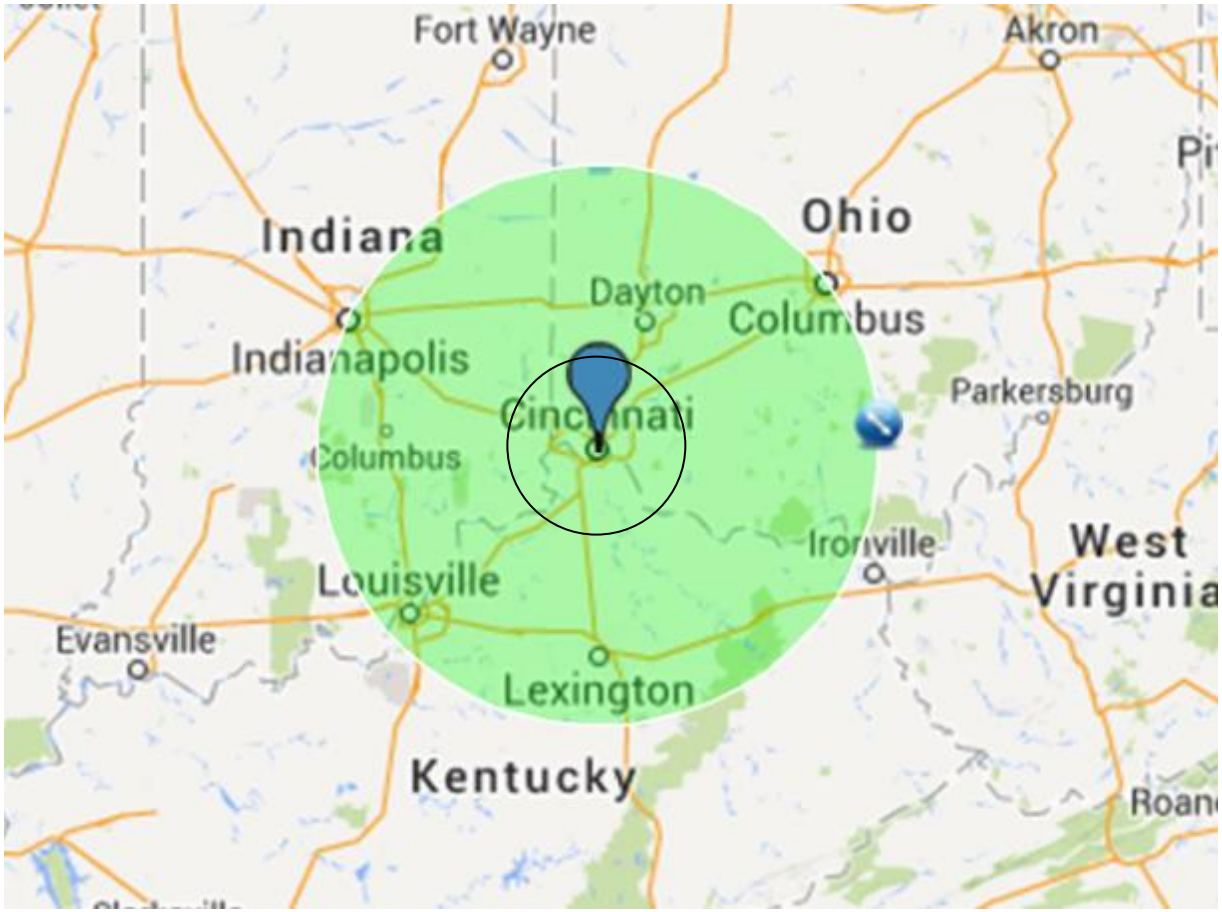
The majority of our patients are local

58% of referrals come from within 30 miles

78% come from within 100 miles



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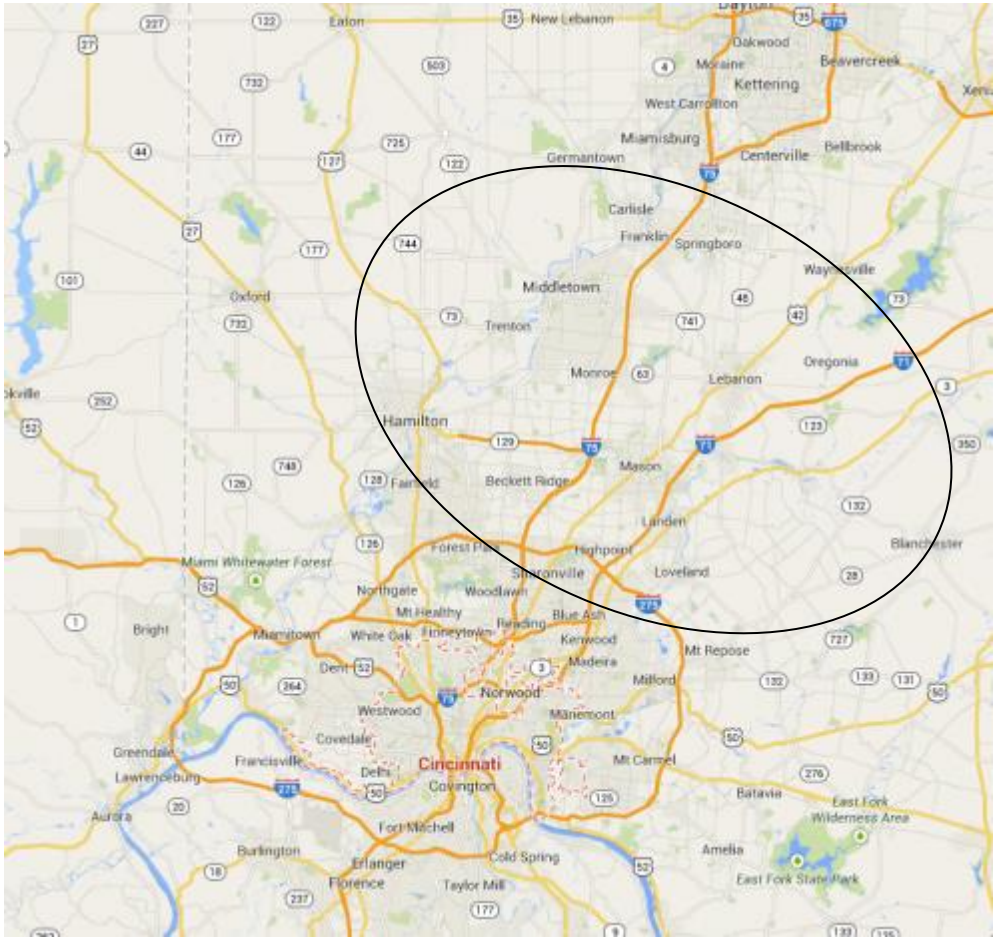
Most common region of referral



- Referral patterns are unevenly distributed.
- Some provider groups are “tuned in.”
- 86 pediatric referrals from population of ~38,000
- Estimate of 0.2%, or 1 in 500 suspected to have EDS-HT.

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How common is EDS-HT?

- It remains unclear
- 1/10,000 to 1/15,000 is an underestimate
- Prevalence seems closer to 1/100 to 1/500.
- Regardless of population estimates, EDS-HT may be overrepresented in certain medical areas
  - Estimated 40% of pediatric pain clinic
  - 33% of adult GI clinic visits (552 evaluations)
    - Clin Gastroenterol Hepatol. 2014 Jan 16
    - doi: 10.1016/j.cgh.2014.01.014

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First step to demystifying EDS

Stop saying “EDS is rare”

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First step to demystifying EDS

Stop saying “EDS is rare”

In doctorspeak, “that’s rare” means:

“I don’t need to think or learn about that.”

“Go talk to a specialist.”

“This is not important enough to include in our teaching curriculum.”

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Next step for demystification: *helpful* model building

- Use research to identify clinical patterns, but use them to build testable models with mechanism and intervention.

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Research at CCHMC

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EDS problems tend to be age dependent and variable

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Preteen problems (< 11 y.o.)

- Hypotonia -- occasional
- “Growing pains”
- Handwriting problems
- Bleeding / bruising
- Occasional:
  - Headaches
  - Postural tachycardia
  - Joint dislocation

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Teenage to adult problems

- Musculoskeletal dysfunction
  - Chronic pain and joint dislocations
  - Temporomandibular joint dysfunction
- Dysautonomia and orthostatic intolerance
- Gastrointestinal dysfunction
- Chronic headaches
  - Tension-type and migraines
- Bruising and bleeding
- Anxiety and panic disorder

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Phases of the condition

Observations from the clinic:

- Childhood
  - mild presentation, flexible
- Teenagers
  - Males—often improve, flexibility decreases
  - Females—accelerate symptoms, flexibility retained and possibly increased. Seems to correlate with menarche. Symptoms can correlate with menstrual cycle
- Adults
  - Flexibility tends to decline
  - 9:1 ratio of affected females to males

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Hypothesis: Male versus female hormones change the quality of connective tissue

- Isn't that obvious? YES!
- Isn't that proven? NO!

- Our approach: Start at the place where we find the biggest change in hormones--puberty.
- Our advantage: Our young population.

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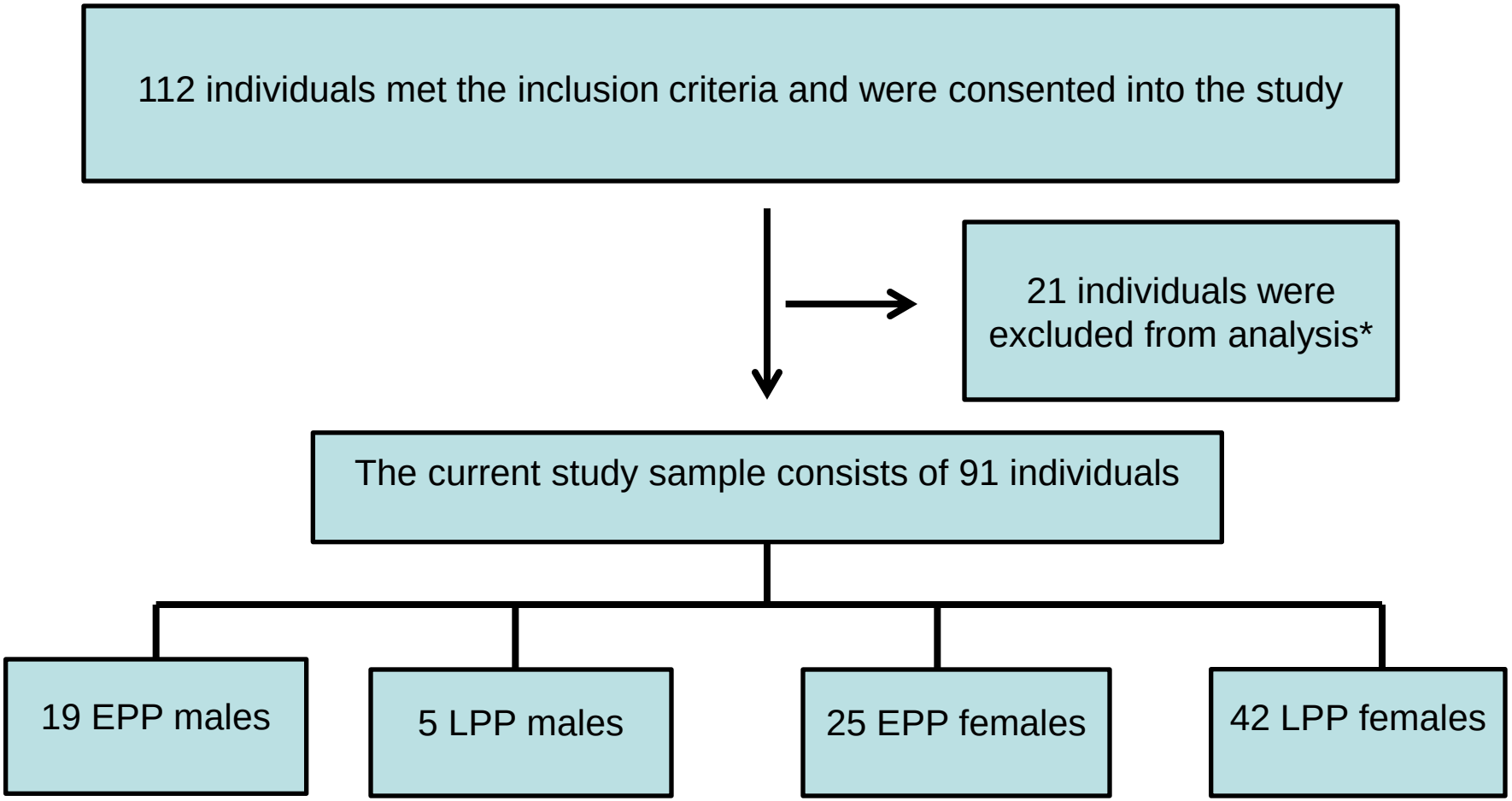
Over 3 months, we collected 91 young patients



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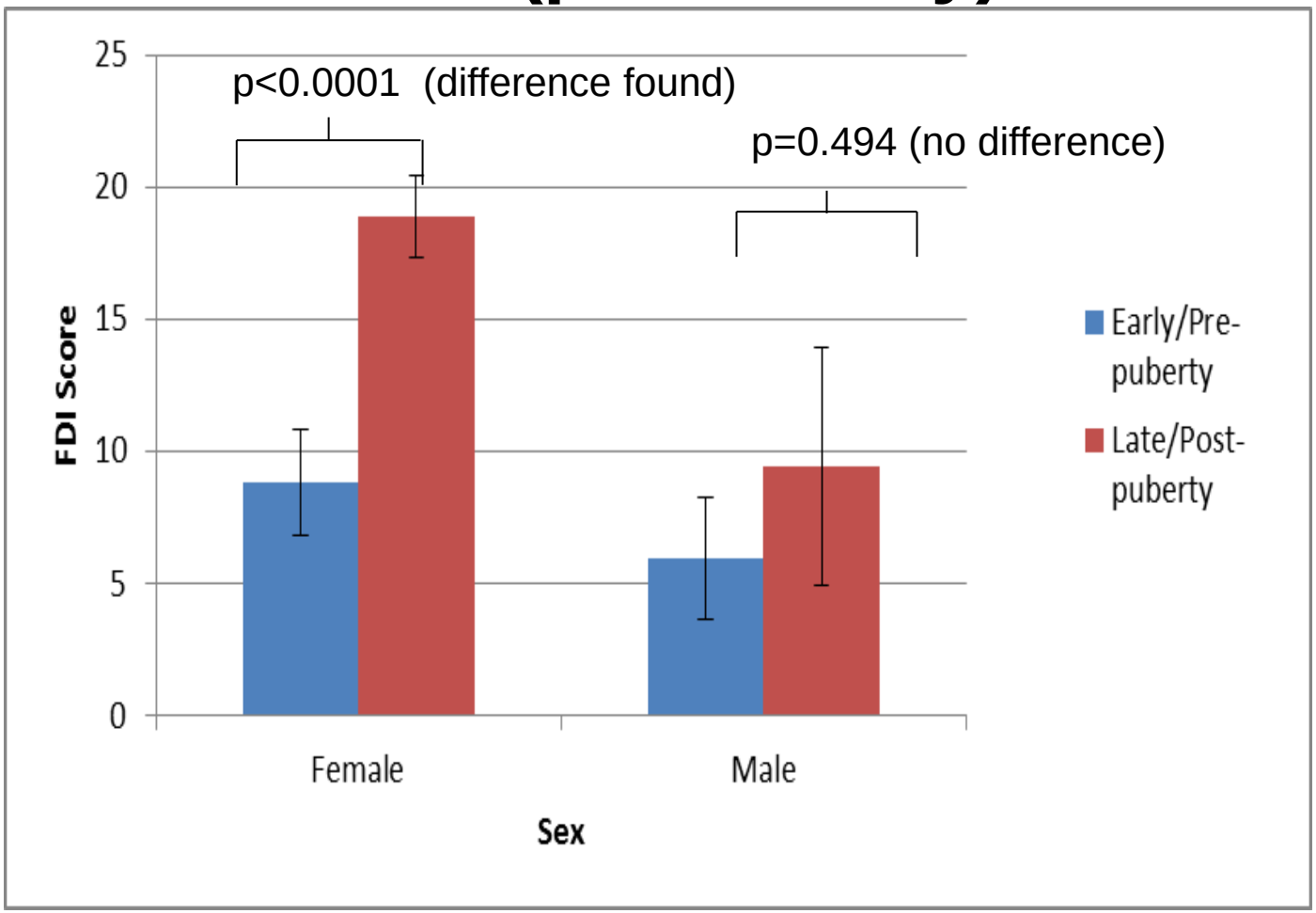
Assessment Tools

- In addition to a study examination, participants were asked to complete a composite questionnaire that included:
  - Tanner puberty scale
  - Functional Disability Inventory (FDI)
  - Pediatric Quality of Life Rheumatology module (PEDSQL)
  - Orthostatic Grading Scale (OGS)
  - Migraine Disability Assessment (MIDAS or PedsMIDAS).

Comparison of Functional Disability Inventories (preliminary)



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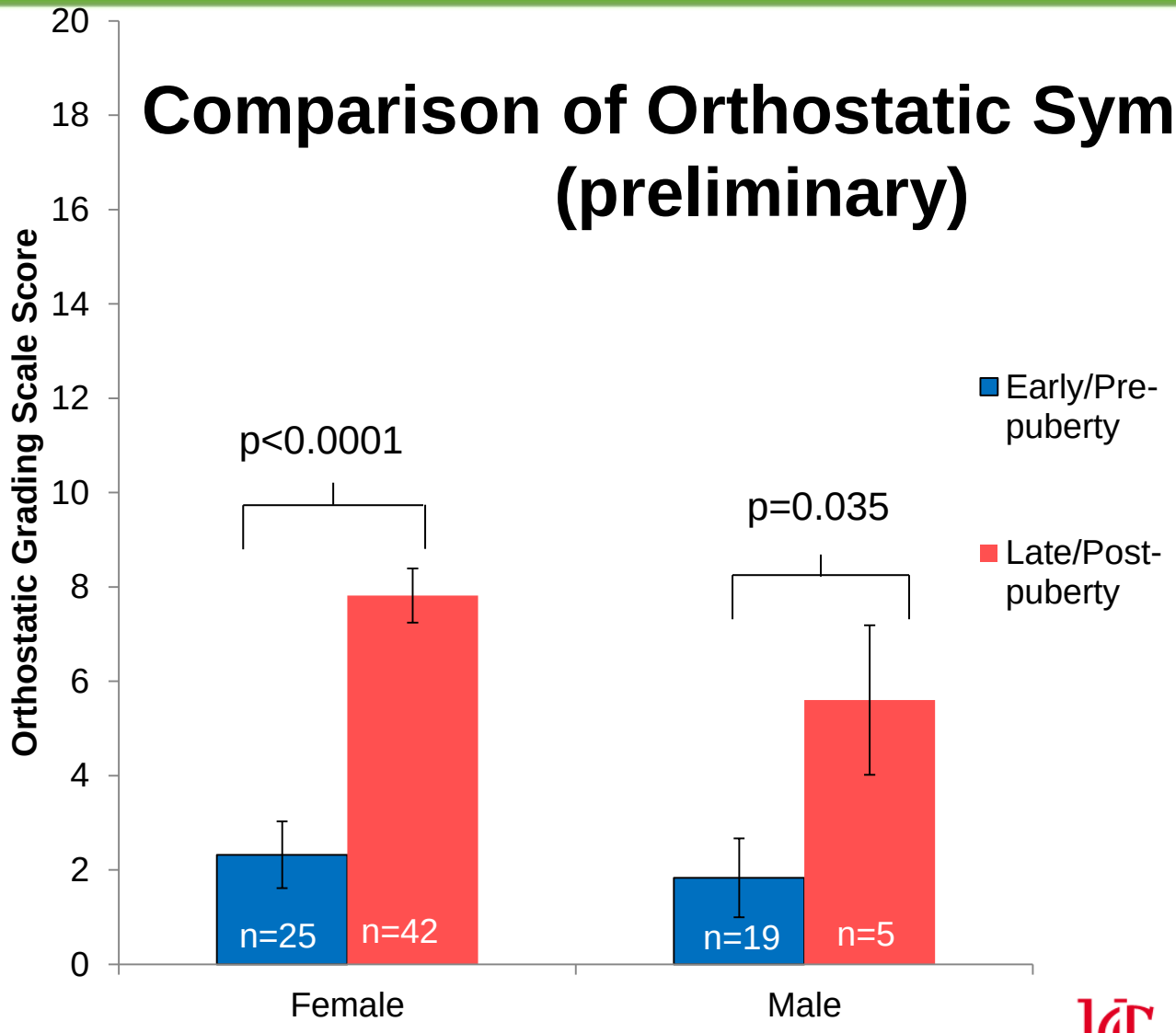
Comparison of Orthostatic Symptoms (preliminary)



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Our data . . .

- Is incomplete for older boys, so data collection is ongoing
- Demonstrates increases in disability and dysautonomia with teenage girls.
- Average age of symptom onset = 11 +/- 1 yrs.
- Average age of menarche = 11 +/- 1 yrs.

- Supports the hypothesis that symptoms are increased by female hormones.
- Does it prove the hypothesis? No.

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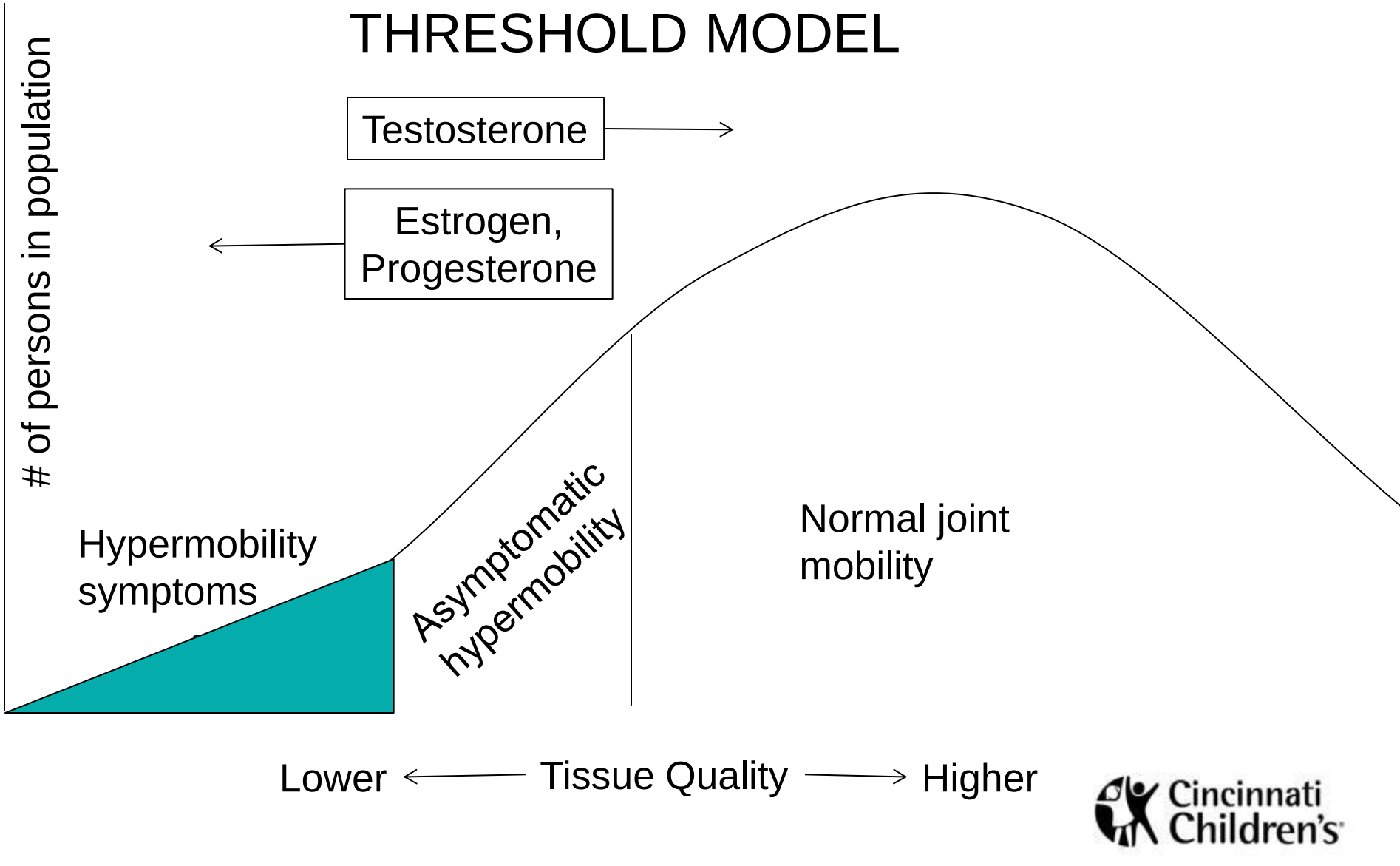
THRESHOLD MODEL



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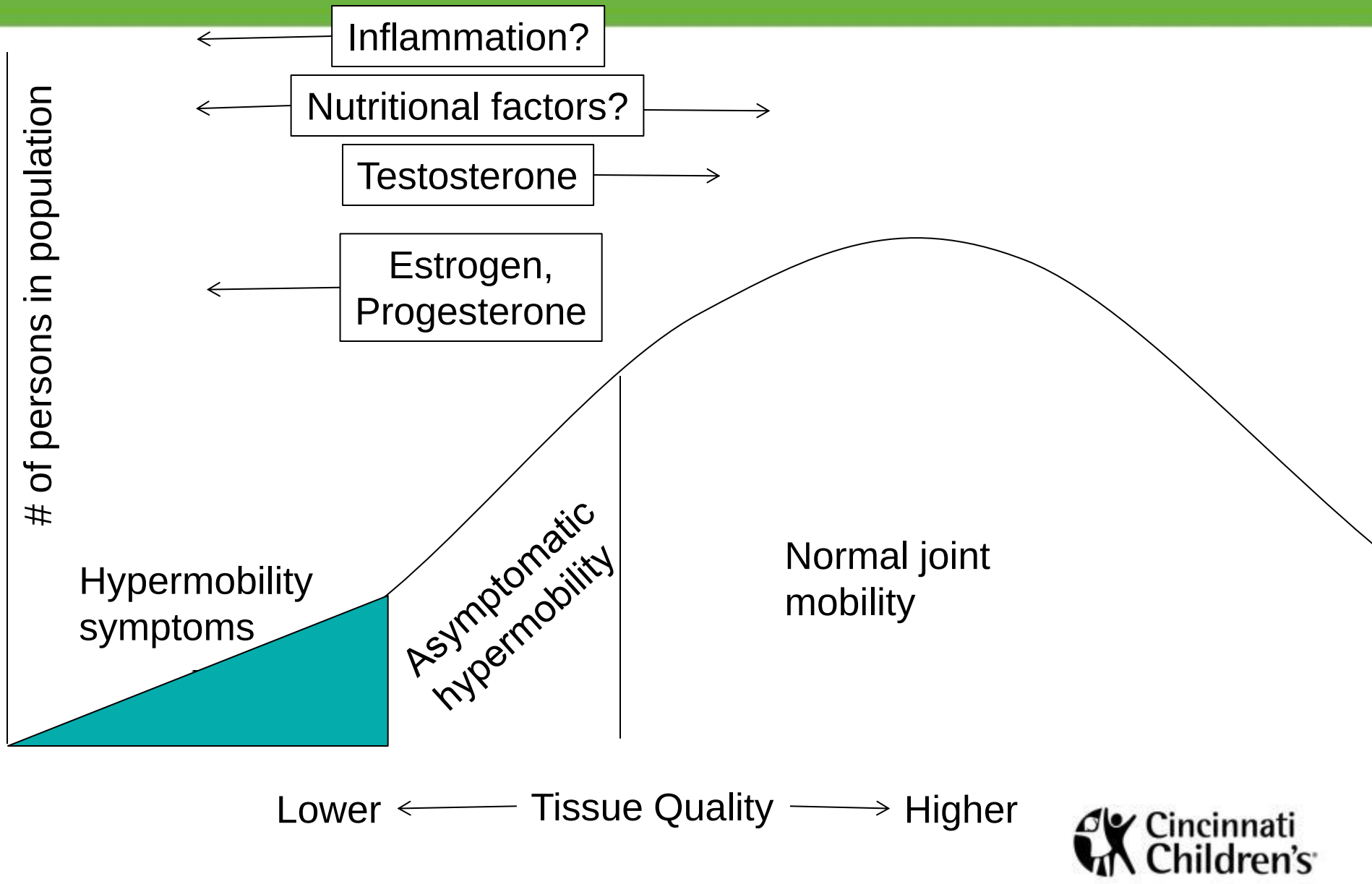
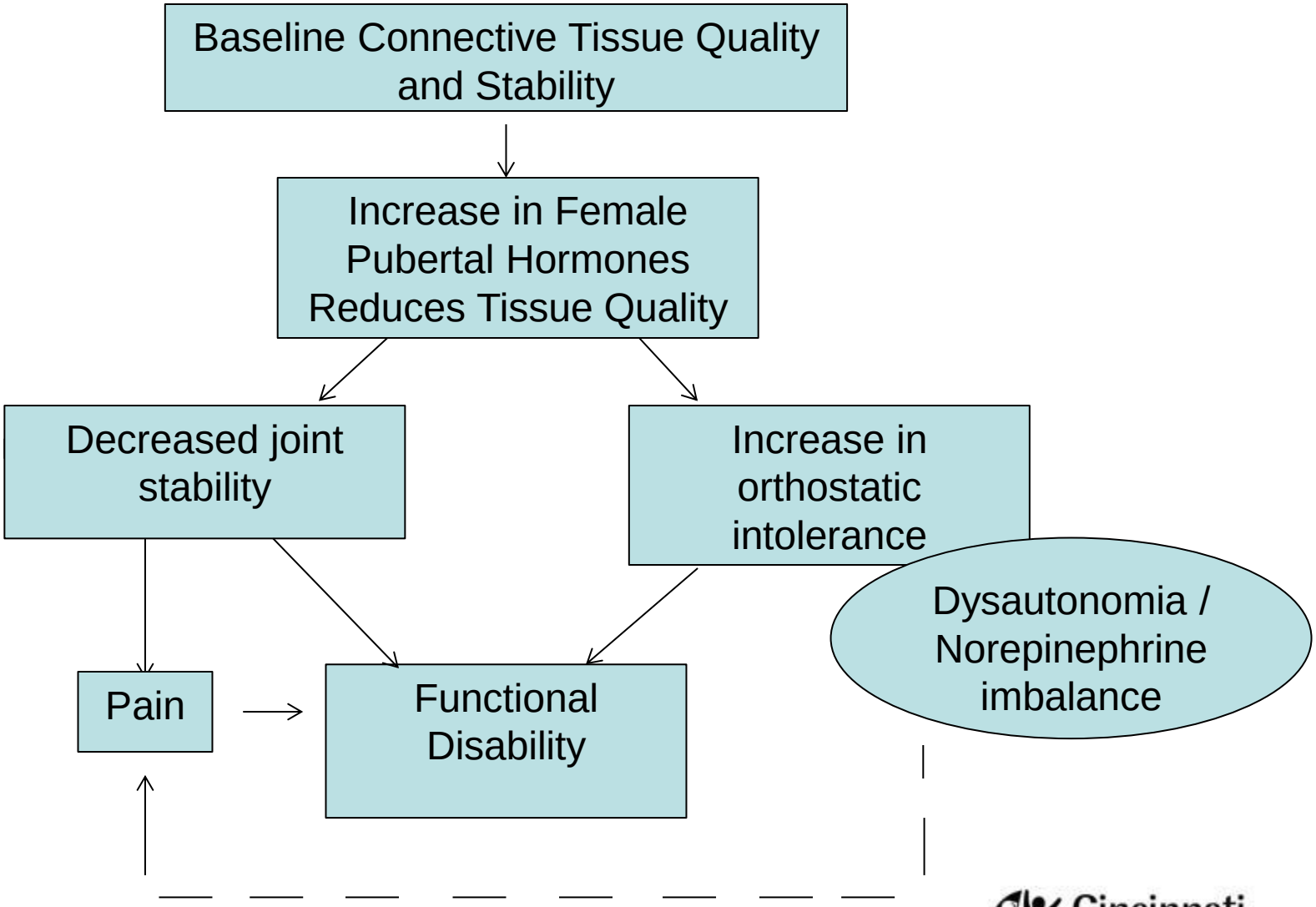

Inflammation?
Nutritional factors?
Testosterone
Estrogen,
Progesterone
# of persons in population
Hypermobility
symptoms
Asymptomatic
hypermobility
Normal joint
mobility
Lower
Tissue Quality
Higher



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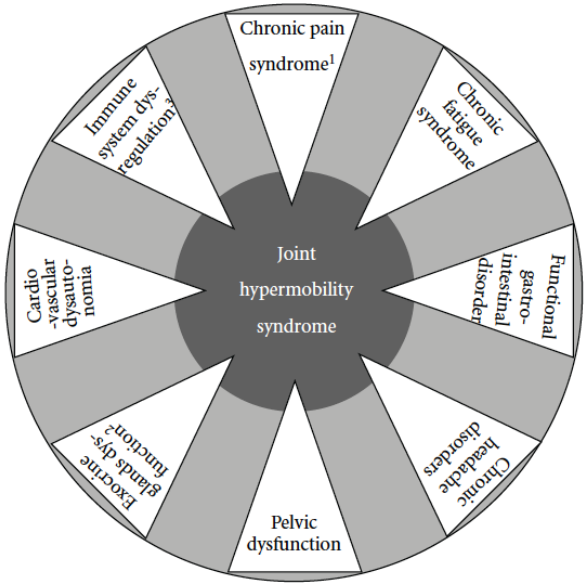
That's a nice model, but where does all this stuff come from?



We need a model of pathogenesis

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Implications of building a model

- A model of association
  - Helps a provider look for other problems, but should serve as a framework for . . .
- A model of pathogenesis
  - Can be tested systematically
  - Guides treatment choices
    - Hierarchies imply that some factors may lie at the root of others. Treat the root cause.
  - Can be better understood by physicians and patients
    - No longer a “collection” of problems

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We have one model of pathogenesis already: Proprioception

- The sense of proprioception is impaired
- Proprioception is spatial awareness and relative positioning of limbs.
- Without it, people tend to run into things, look clumsy as kids, have difficulty walking up and downs stairs at night . . .

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Altered proprioception in EDS

- A recent metaanalysis confirmed
  - poorer lower limb joint position sense (JPS) ($p < 0.001$)
  - Increased threshold detection to movement ($p < 0.001$)
  - Difference in finger positional sense ($p < 0.001$)
- Static postural control is impaired
  - More postural sway
  - More concentration required to stabilize

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Rheumatol Int. 2013 Nov;33(11):2709-16. doi: 10.1007/s00296-013-2790-4. Epub 2013 Jun 1.
Res Dev Disabil. 2013 Feb;34(2):840-6. doi: 10.1016/j.ridd.2012.11.007. Epub 2012 Dec 12.

Where does proprioception come from?

- Mechanoreceptors
  - Nerve fibers that sense stretch
- The sensory apparatus is a filament-like structure that stretches and contracts
- As the length of the fiber changes, so does the nerve firing rate.
- By comparing the stretch and tension of various muscle groups, the brain interprets relative body position

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Altered proprioception

- While not proven, it can be argued that altered connective tissue impairs the ability of mechanoreceptors to accurately respond to changes in stretch.

- In other words, anything that uses the “stretch” with EDS probably does not work right.

- Remember this conceptual model:
  - “Sensory mechanisms based on stretch are likely impaired”

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Dysautonomia

- Autonomic nervous system controls all the unconscious functions
  - Breathing, heart rate, blood pressure, alertness
- Two halves:
  - Sympathetic
    - Activation state: “Fight or flight”
  - Parasympathetic
    - Resting and repair state: “Rest and digest”

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Dysautonomia

- Commonest symptom—feeling faint or "blacking out" with standing
- Gazit, et al 2003
  - 27 JHS vs. 21 controls, >90% female,
  - Mean age 32 years.
  - 78% had some degree of orthostatic autonomic dysfunction compared to 10% in controls.
- Syncope, orthostatic intolerance and postural orthostatic tachycardia (POTS--increase of HR by 30, with less than 20/10 BP drop)

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Newer dysautonomia research

- Similar results
  - “EDS” instead of “Hypermobility syndrome”
- Decreased central responsiveness to sudden shifts in blood pressure
- Increased *peripheral sympathetic activation*

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Dysautonomia and the brain

- Patients with POTS have poor sleep efficiency
  - Anectodal evidence of sympathetic activation during sleep
- Symptoms of racing heart beat related to POTS may be interpreted as anxiety or panic
  - Orthostatic changes may not be the only trigger
- Poor sleep and anxiety may augment each other

Auton Neurosci. 2013 Oct;177(2):260-5. doi: 10.1016/j.autneu.2013.02.021. Epub 2013 Mar 26.

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Sympathetic effects

- Increased sympathetic activation would be a good explanation for
  - Racing heart beat
  - Anxiety
  - Panic
  - Sleep dysfunction

(we've seen this talk before . . .)

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How could all these sympathetic effects come about?

- Hypothesis: Aberrant baroreceptor function causes dysregulation of norepinephrine release
- Baroreceptors are just like the muscle stretch receptors, except that they are wrapped around arteries and register blood pressure.
- With every heartbeat, norepinephrine is released to help regulate blood pressure.

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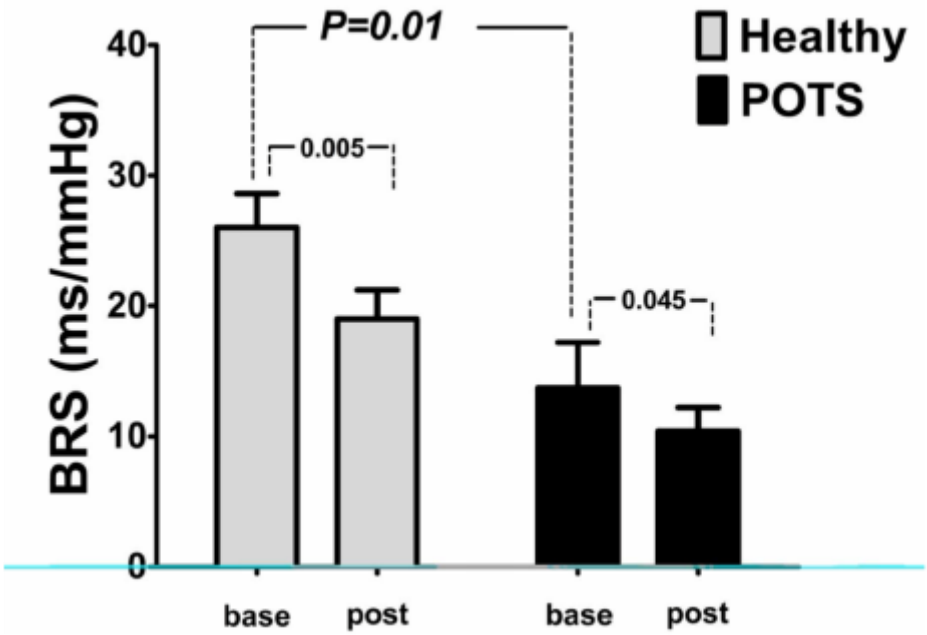
Impaired baroreceptor responsiveness in POTS

- BRS directly related to arterial compliance—the “elasticity” of the vessel wall.
- With POTS, BRS decreased
- This has not been demonstrated in EDS—lots of technical problems



Circ Arrhythm Electrophysiol. 2012 Feb;5(1):173-80. doi: 10.1161/CIRCEP.111.965343. Epub 2012 Jan 13.

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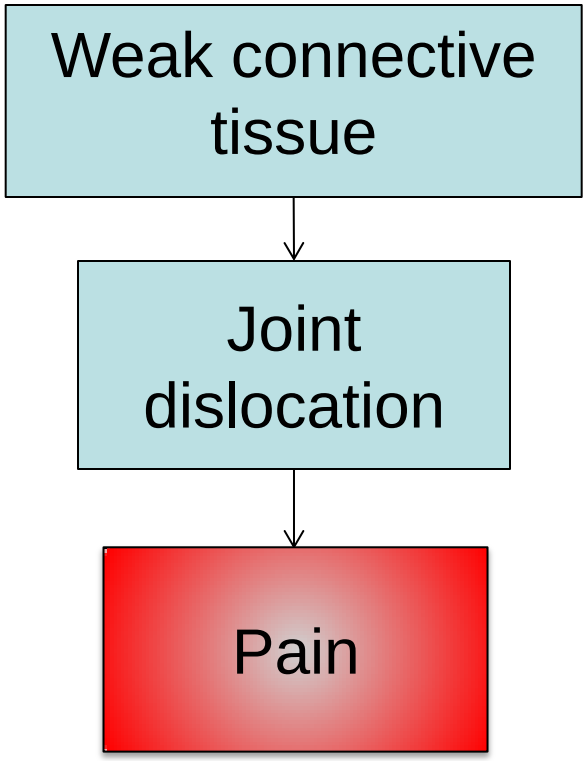
The old model



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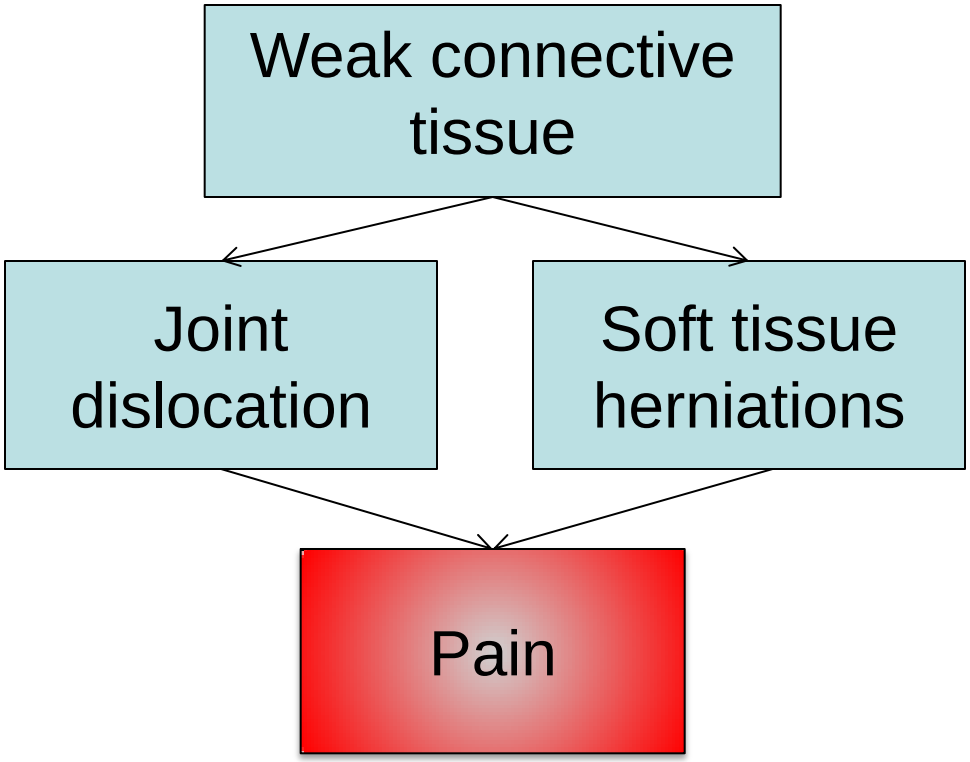
The old model (revised)



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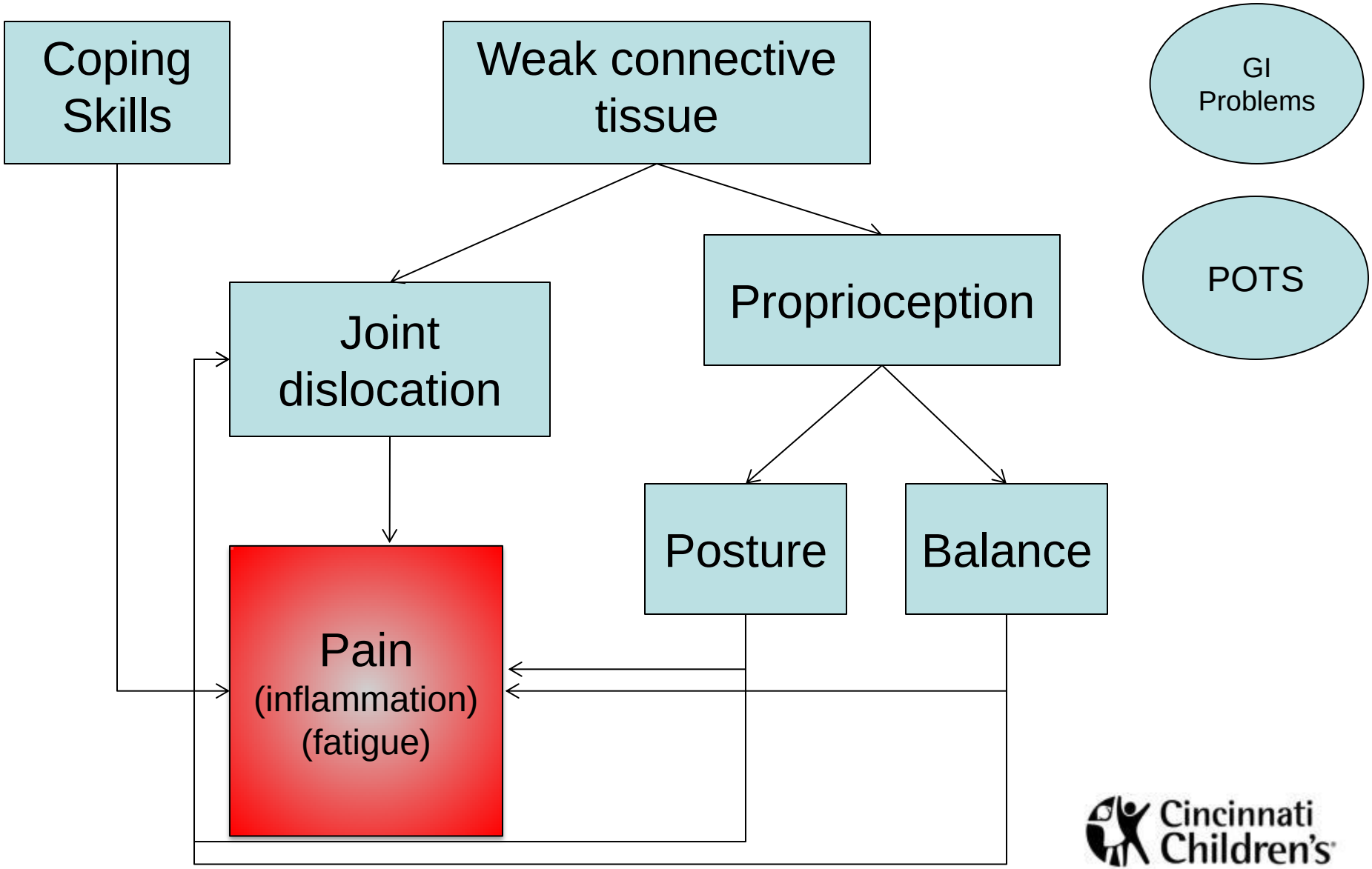
The current model



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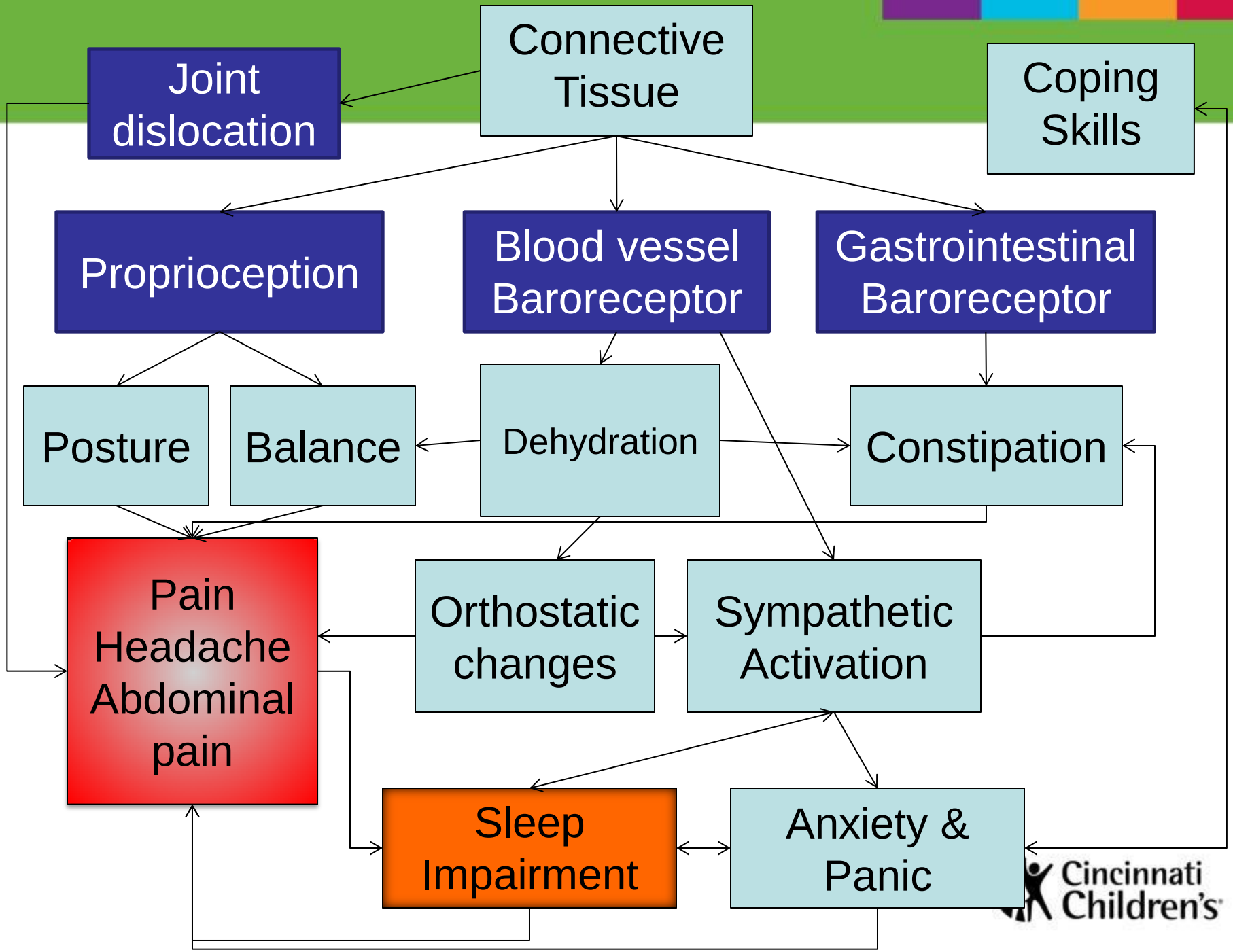
Connective Tissue
Joint dislocation
Coping Skills
Proprioception
Blood vessel Baroreceptor
Gastrointestinal Baroreceptor
Posture
Balance
Dehydration
Constipation
Pain Headache Abdominal pain
Orthostatic changes
Sympathetic Activation
Sleep Impairment
Anxiety & Panic
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Questions?

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