Smooths, splines, and the chamber of secrets: Demystifying female reproductive health

Ipek Ensari, PhD

May 16th, 2024

NY R Conference, New York

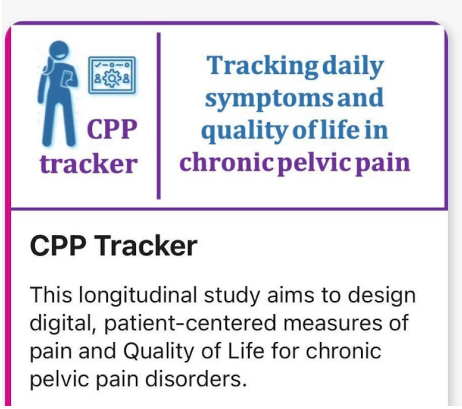
HPI·MS Mount Sinai

Hasso Plattner Institute for Digital Health at Mount Sinai

Disclosures

COI - None.

Funding: NIH/NICHD (1R01HD108263)



Collaborators: Emily Leventhal, BS; Nivedita Nukavarapu, PhD



Female Chronic Pelvic Pain Disorders (CPPDs)

- CPPDs - Prevalence: 1 in 7
  - ~50% of cases remain undiagnosed, difficult to pinpoint underlying cause
  - Top indication for referrals (20%) in outpatient 2° care appointments
- Comorbidities
  - Musculoskeletal pain and dysfunction in 50-90%
  - Depressive and anxiety disorders twice as likely
- Among top contributors to disease burden
  - disability + work productivity loss, direct and indirect costs, inadequate insurance coverage
- Poor prognosis
  - ~17% resort to chronic opioid use, 2nd top indication for hysterectomies
  - Symptom/disease self-management (SM)

Published online 2023 Feb 9. doi: 10.1371/journal.pone.0269828 PMID: 36757947

The burden of Chronic Pelvic Pain (CPP): Costs and quality of life of women and men with CPP treated in outpatient referral centers

David Hutton, Supervision, Visualization, Writing – review & editing, [1] Aida Mustafa, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, [2,3] Soha Patil, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing, [2,3] Saira Rathod, Methodology, Resources,

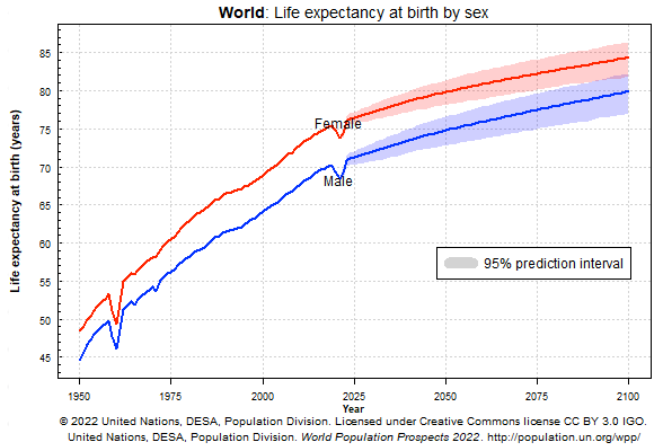
WHO systematic review of prevalence of chronic pelvic pain: a neglected reproductive health morbidity

Pallavi Latthe, Manish Latthe, Lale Say, Metin Gülmezoglu & Khalid S Khan

BMC Public Health **6**, Article number: 177 (2006) | Cite this article

Background

Health care planning for chronic pelvic pain (CPP), an important cause of morbidity amongst women is hampered due to lack of clear collated summaries of its basic epidemiological data.



Augmenting data sources on CPPDs

- Direct patient input from mHealth sources
  - Self-tracked (e.g., via Apps)
  - Passive data (e.g., wearables, sensors)
  - Capture real-world data to inform decision making, prediction, evidence generation
- Routine outcome monitoring of responses outside of the clinic
  - Tracking treatment and self-management (SM) effects/responses
  - Combine self-reported and passively-obtained data
- SM support

– Most frequent chronic care model intervention, associated with significant improvement measured by patient-level outcomes



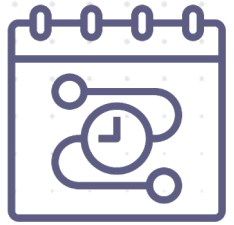




Working with mHealth data

mHealth-based patient-reported and passively obtained data differ in attributes:

- Temporal complexity (frequently sampled) - variable
- Timing of ambulatory monitoring?
- Multi-modality – how to harmonize
- Meaningful summarization
- Aggregation leads to loss of information (symptom trajectory as a scalar vs curve)
- Missingness – variable









Objectives and Approach

Questions:

1) Can we effectively analyze multi-modal data to identify associations between chronic symptoms and lifestyle factors in CPPDs?

Techniques and measures:

- “multi-modal data" - different data types (clinical data, self-reported symptoms, lifestyle factors)
- Measures: symptoms and health behavior (e.g., physical activity and exercise)





Exercise as pain self-management

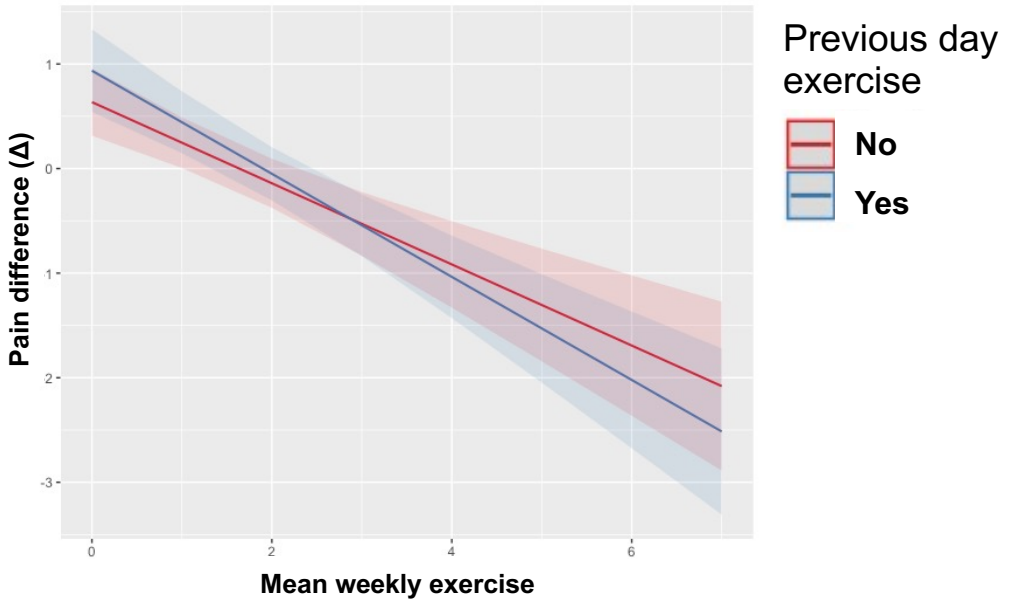
- Relevance for tailoring care in CPP disorders - Determine level of “precision” needed

  CPPDs

  PA volume across clusters similar to general population

  40% of the population likely “low active or sedentary”

  Increased risk of adverse health outcomes

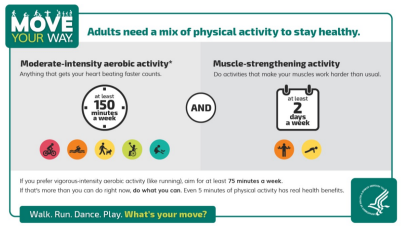


Moderating effect of weekly exercise levels on the previous-day exercise on change in pain. Shading around the lines represent 95% confidence intervals (Ensari et al., 2022)

Healthy Adults[a]		
Steps/day Zone	Descriptive Category	Steps/day Zone
		≥14,500
≥12,500	Highly active	12,000–14,499
10,000–12,499	Active	9500–11,999
7500–9999	Somewhat active	7000–9499
5000–7499	Low active	<7000
<5000	Sedentary	

[a] Based on the compiled evidence presented in Tudor-Locke and Bassett (36).
[b] Based on a criterion presented by Tudor-Locke et al. (42).

Tudor-Locke et al. 2012



USDHH

Methods

Sample, Analysis



Study Sample and Data

- Sample:

- Individuals living with CPP disorders (N= 68)

- 4,159 person-level days of data

- Mostly employed (N=51; 76%), urban-dwelling (N=56; 84%), median age = 36 years (18 - 54)

Data sources and structure:

- Self-tracked symptoms from weekly questionnaires

(standardized, validated, clinical benchmarks)

- Passively-obtained daily PA from activity trackers



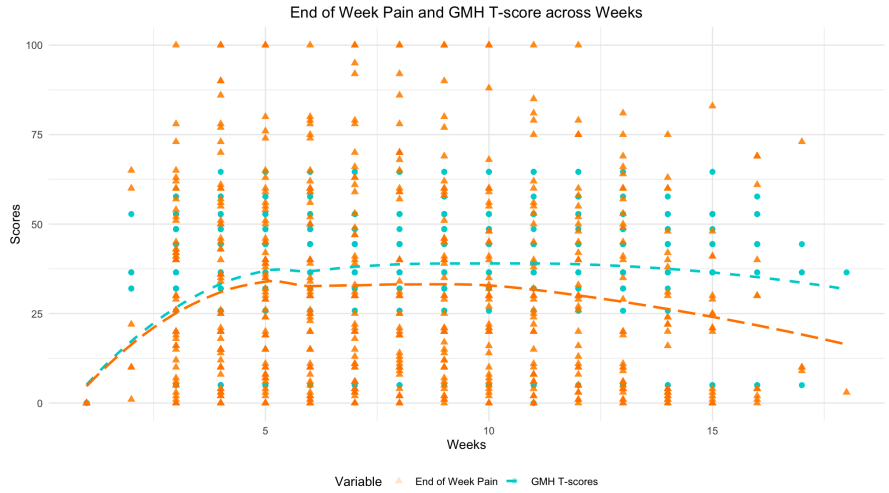


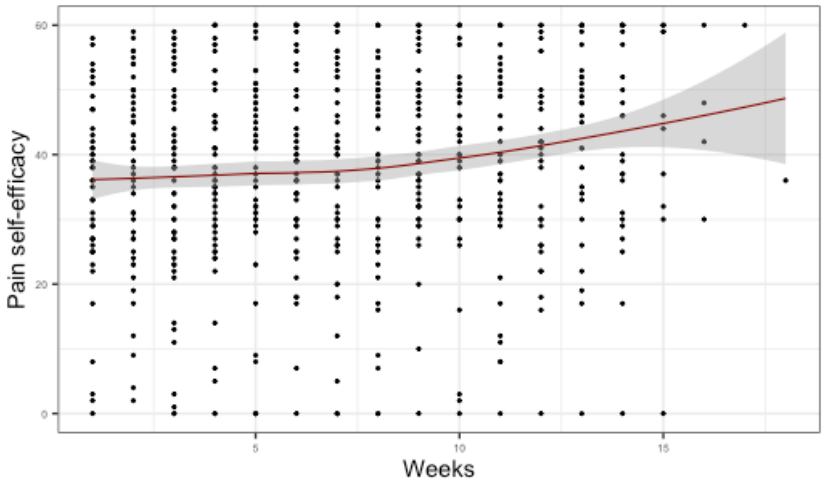
Table 1: Descriptive Statistics for Overall Population

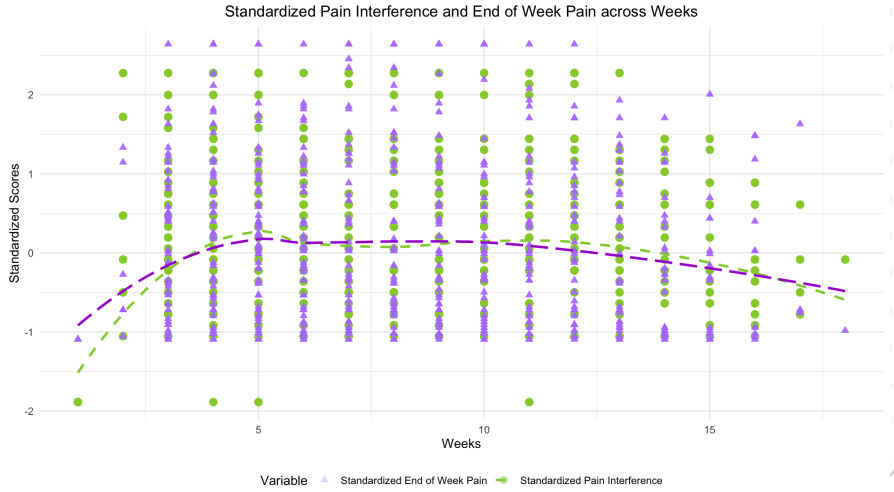
Characteristic	N = 68[1]
What is your ethnicity?	
Hispanic or Latino	17 (25%)
Not Hispanic or Latino	47 (70%)
Unknown	3 (4.5%)
What is your race?	
Asian	7 (10%)
Black	12 (18%)
Unknown	10 (15%)
White	38 (56%)
White and Black	1 (1.5%)
What is your highest level of education?	
High_school	3 (4.4%)
Some_college	5 (7.4%)
College_degree	59 (87%)

Day-to-day variations – mHealth data

Outcome	ICC	Within σ2	Between σ2
PROMIS GMH	0.648	1.461	2.69
MPQ current pain	0.62	275.56	463.39
Pain Interference	0.581	18.38	25.49
PROMIS Physical Function	0.685	4.19	9.15
Pain Self-efficacy	0.727	64.96	173.60
Steps	0.364	19840219	11403449
Moderate to vigorous PA (MVPA)	0.290	2068	848







Study Sample and Data (cont.)

participant_num	weekn	gmh_tot	pseq_tot	mvpa_1	mvpa_2	mvpa_3	mvpa_4	mvpa_5	mvpa_6	mvpa_7
17	2	7	43	109	66	96	88	0	54	86
17	3	6	49	19	55	91	99	64	55	14
17	4	6	45	0	23	0	0	10	0	26
17	5	8	50	50	134	24	59	70	67	99
17	6	8	56	0	12	82	156	116	0	0
17	7	8	56	21	110	116	72	43	65	72
17	8	8	50	29	36	39	0	0	20	42
17	9	4	50	16	114	92	51	31	0	95
17	10	8	50	0	22	49	19	69	82	26
17	11	6	50	21	51	94	0	0	79	96
17	12	8	60	0	41	74	29	46	70	47
17	13	8	52	13	0	63	0	84	73	59
18	2	7	24	38	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*
18	3	7	34	76	0	55	0	*NA*	*NA*	*NA*
18	4	7	29	24	17	71	28	53	61	18
18	5	7	31	10	28	37	103	29	*NA*	*NA*
18	6	8	21	30	30	39	27	182	42	60

Data considerations:

-Missingness

-Sampling time points

-Repeated measures

-Variance in Y ~ X estimates (Random effects)

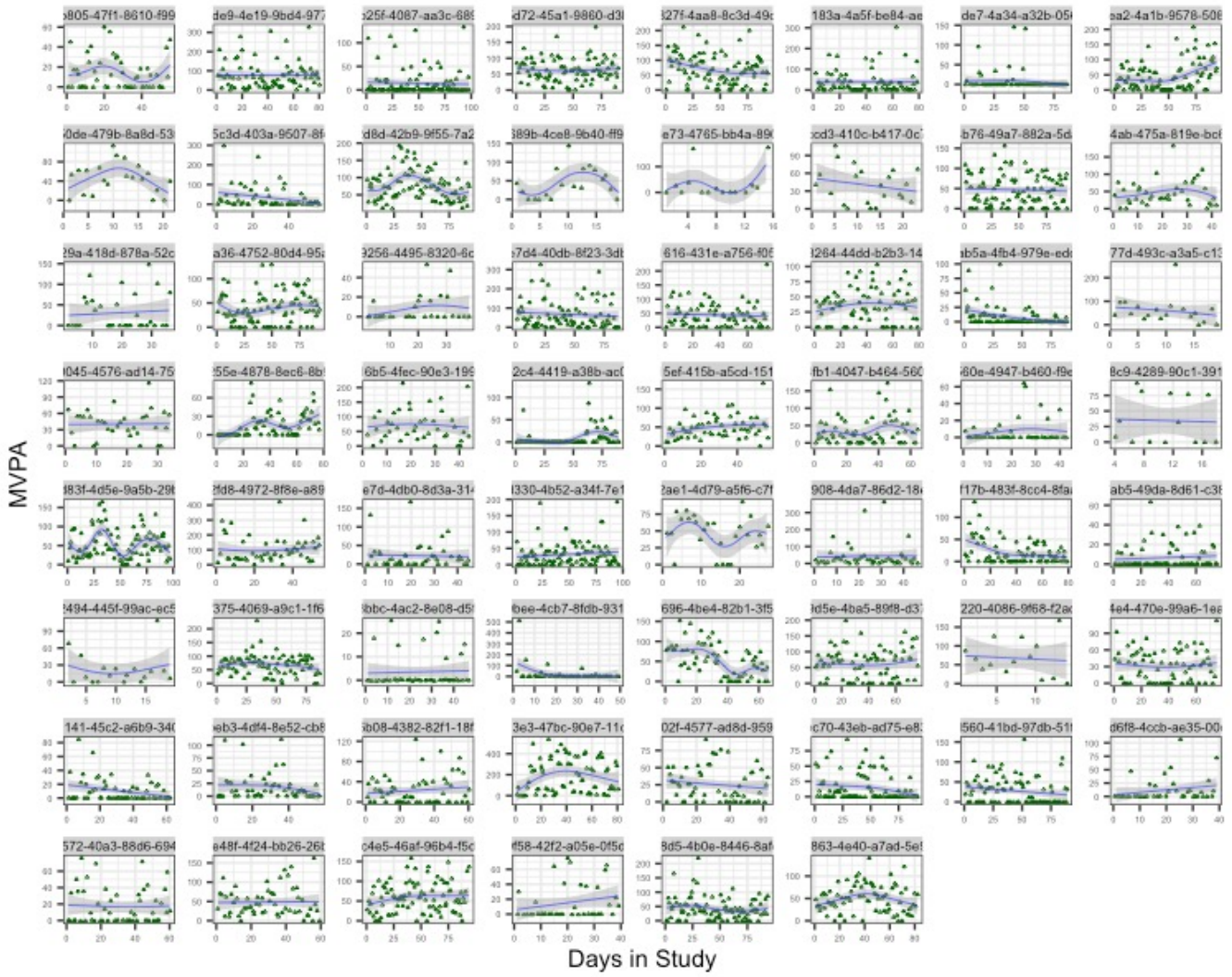
Day-to-day variations – mHealth data (cont.)

- Research Question:

How does daily physical activity (i.e., moderate-to-vigorous PA; MVPA or steps) influence weekly pain and mental health symptoms in CPPDs?

- Statistical Framework:

- Account for individual-level variation
- Random effects modeling
- Account for non-linear relationships
- Smoothing functions for weekly trends



Analytic Approach – smoothing functions

- Generalized Additive Mixed Models (GAMMs) (**mgcv** library - *Wood, 2017*)

- Capture complex (i.e., non-linear) relationships by fitting a non-linear smooth function through the data, while controlling how wiggly the smooth can get
- Define basis functions to estimate the smooth function

- Linear penalized functional regression (LPFR) (**refund** library - *Goldsmith et al., 2012*)

- Allows scalar responses and functional predictors

  1) truncated set of K-L vectors to represent the predictor functions
  2) express the regression function using a spline basis
  3) fit longitudinal model via mixed-model framework (i.e., subject-specific random effects)

Analytic Approach – Outcomes and Predictors

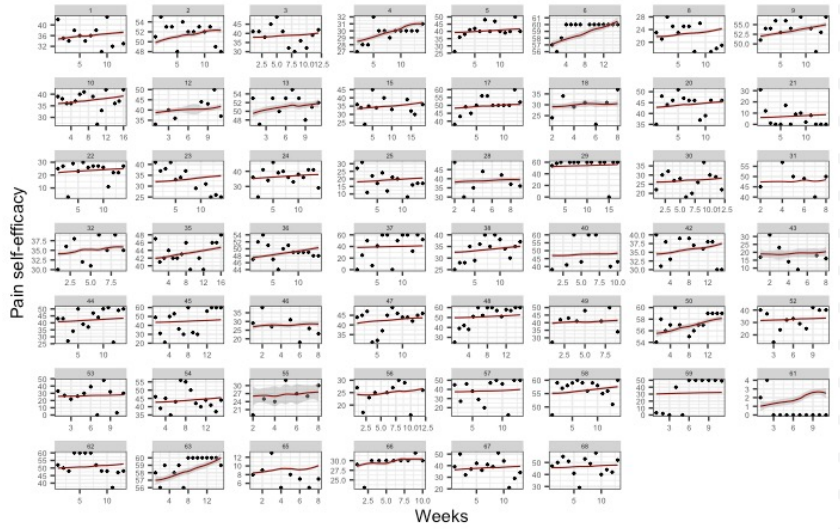
- Generalized Additive Mixed Models (GAMMs) (**mgcv** library - *Wood, 2017*)

  - PROMIS global mental health (GMH); MVPA as the main predictor of interest

- Linear penalized functional regression (LPFR) (**refund** library - *Goldsmith et al., 2012*)

  - Pain Self-Efficacy (PSEQ), steps as proxy for overall weekly activity volume

  - Adjust for covariates (time in study, natural time – cyclical encoding, end of week pain (“current pain”), physical function

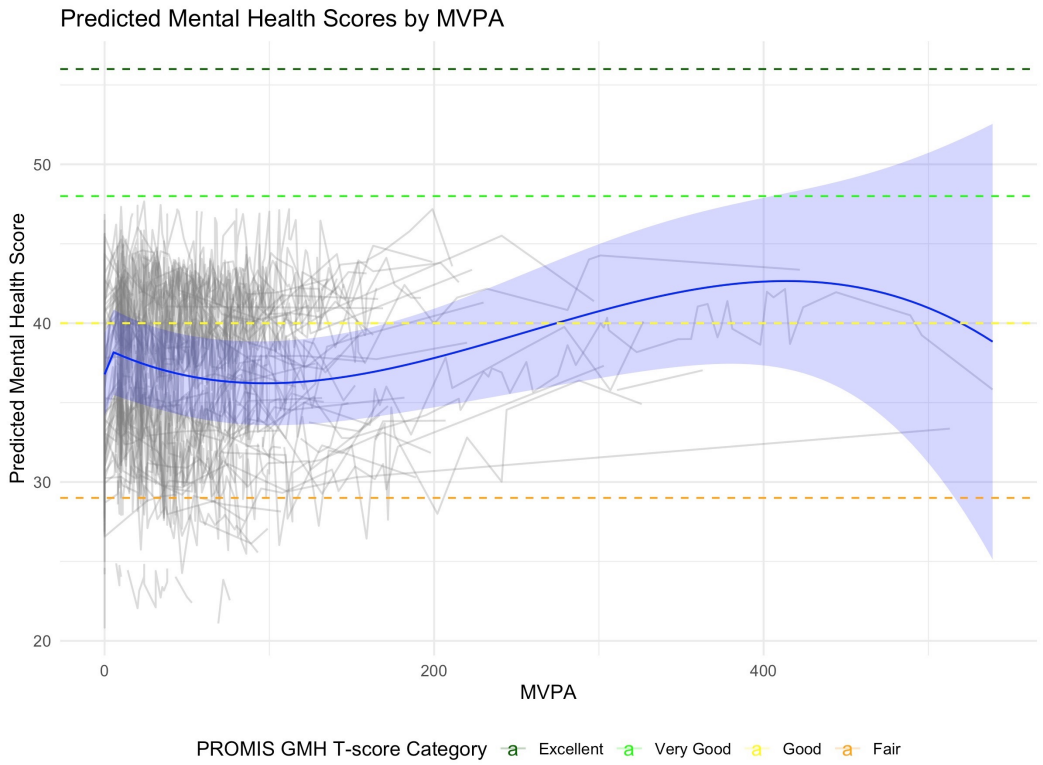


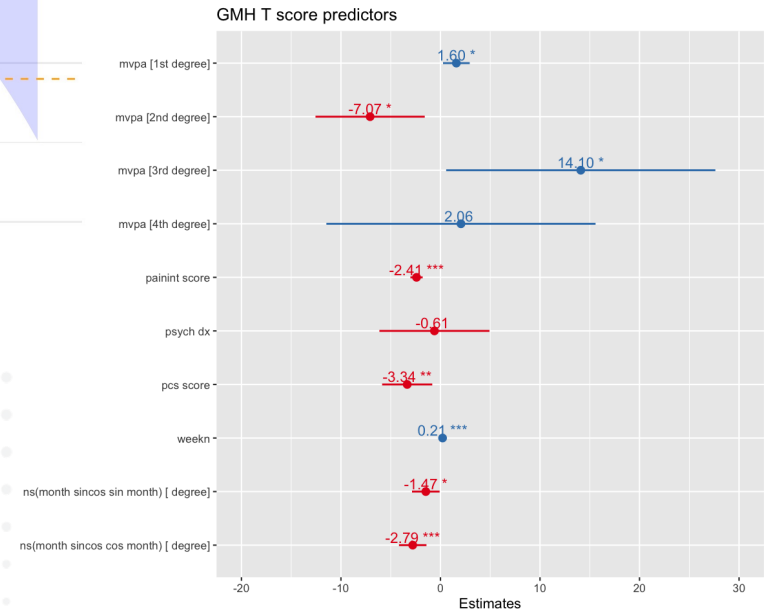
Results

Group-level average effects

Between individual variations

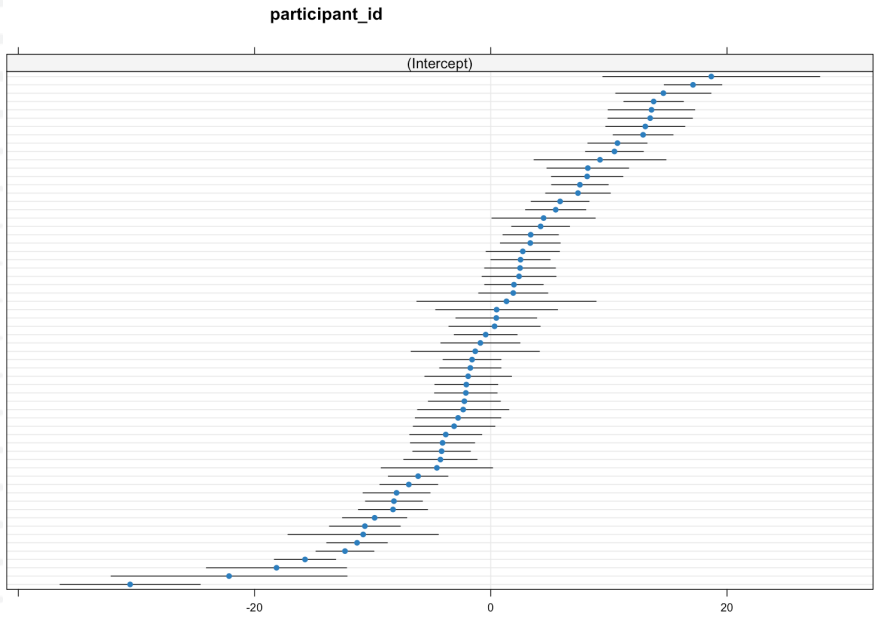
Weekly MVPA and mental health ratings





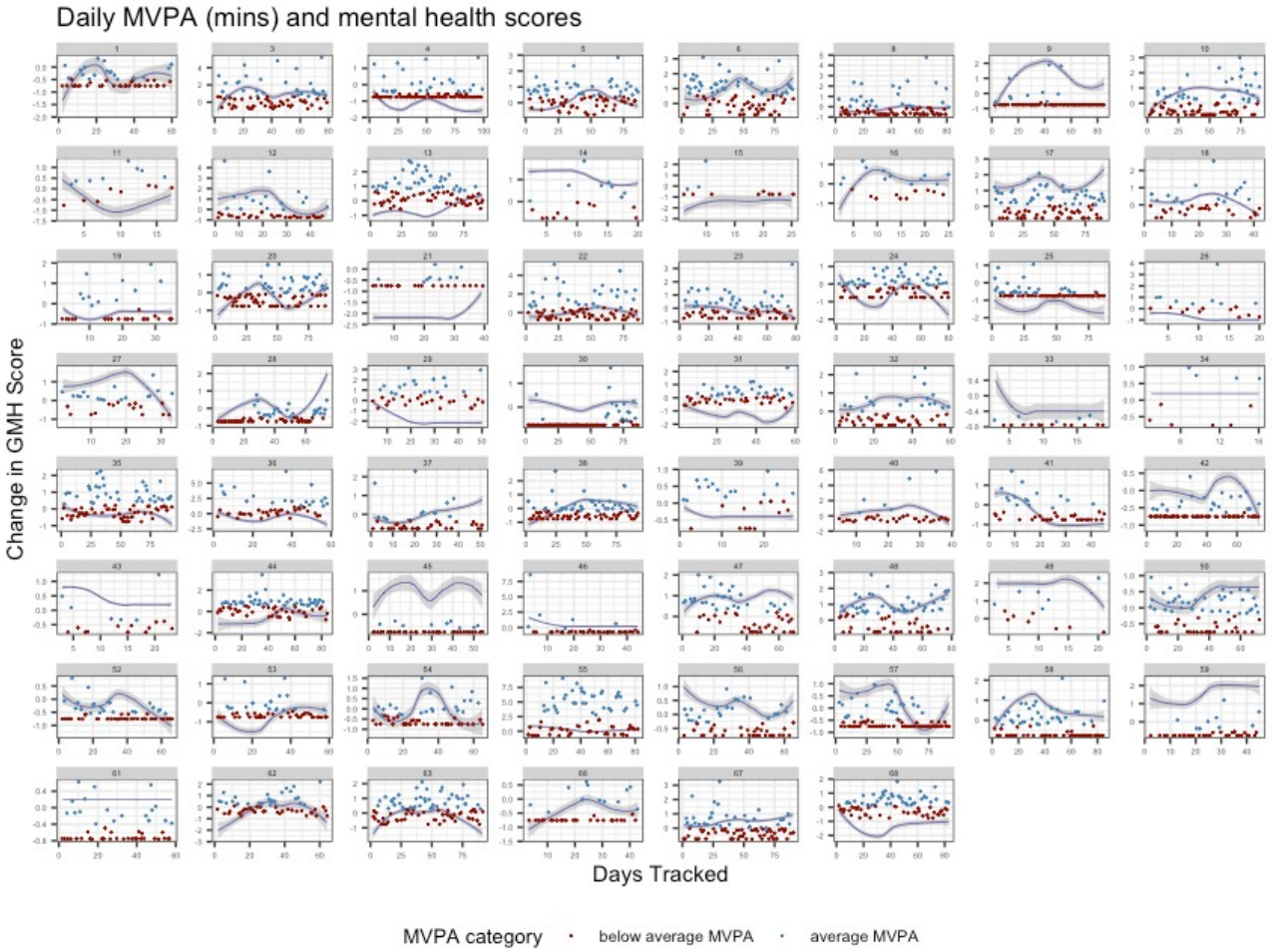
		gmh tscore	
Predictors	*Estimates*	*CI*	*p*
(Intercept)	37.05	33.82 – 40.28	**<0.001**
mvpa [1st degree]	1.60	0.26 – 2.94	**0.019**
mvpa [2nd degree]	-7.07	-12.56 – -1.58	**0.012**
mvpa [3rd degree]	14.10	0.57 – 27.62	**0.041**
mvpa [4th degree]	2.06	-11.47 – 15.58	0.765
painint score	-2.41	-3.02 – -1.79	**<0.001**
psych dx	-0.61	-6.14 – 4.92	0.830
pcs score	-3.34	-5.86 – -0.82	**0.009**
weekn	0.21	0.09 – 0.33	**0.001**
ns(month sincos sin month) [degree]	-1.47	-2.86 – -0.09	**0.037**
ns(month sincos cos month) [degree]	-2.79	-4.17 – -1.41	**<0.001**

Weekly MVPA and mental health ratings

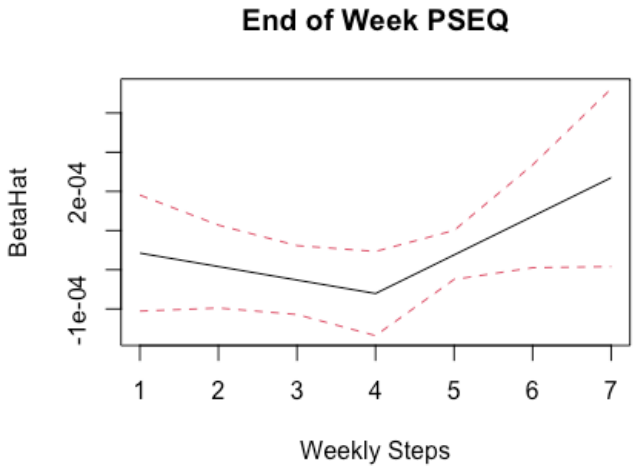


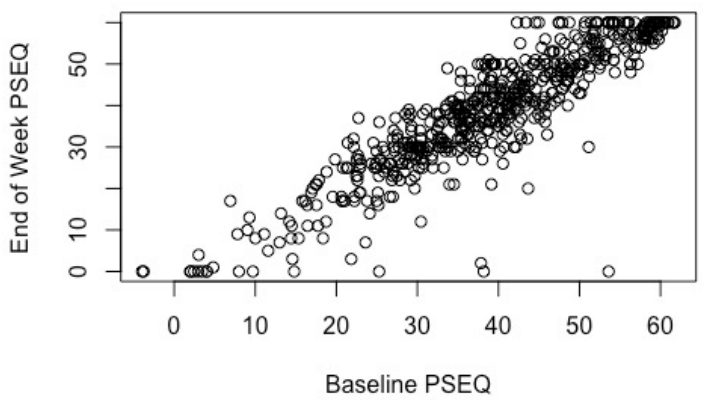
Random Effects

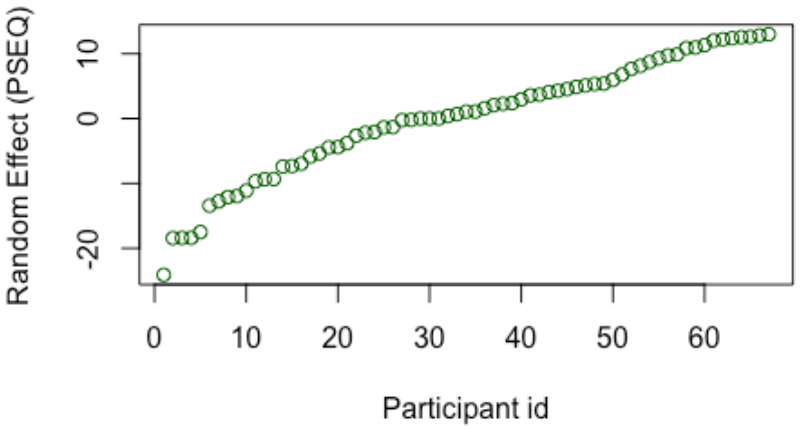
σ^2	142.08
$\tau_{00\ participant_id}$	97.10
ICC	0.41
$N_{\ participant_id}$	62
Observations	3640
Marginal R^2 / Conditional R^2	0.096 / 0.463



Weekly steps and Pain Outcomes



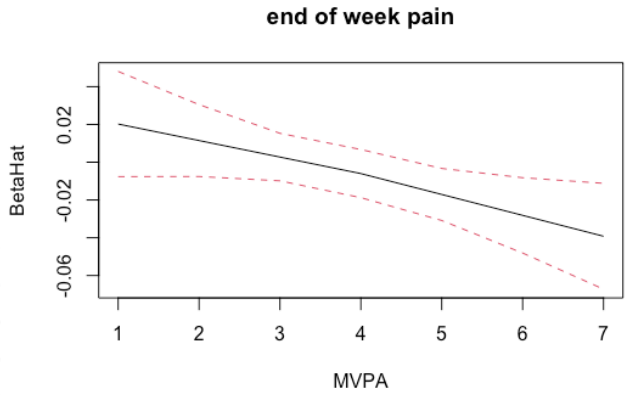




LPFR:
Parametric coefficients:

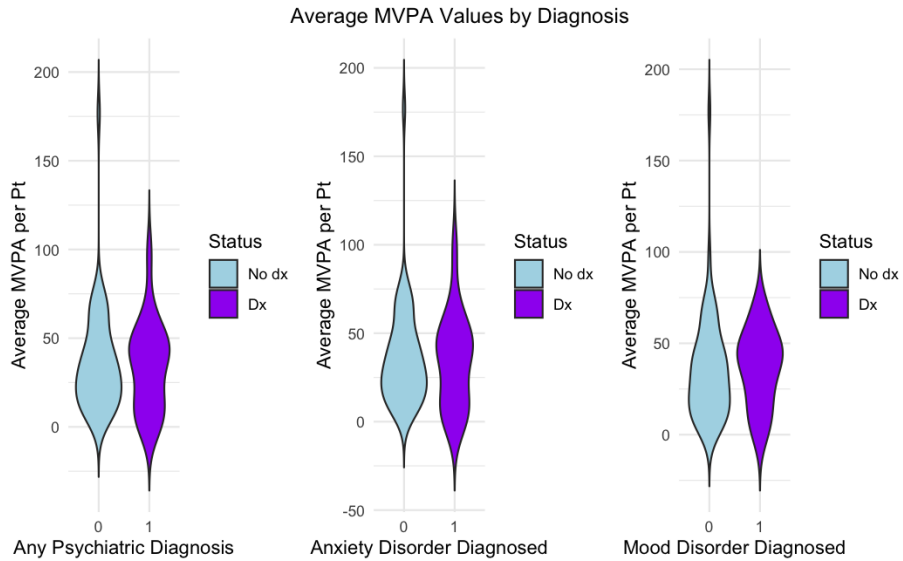
	Estimate	Std. Error	t value	Pr(>|t|)
Intercept	3.38	3.00	1.12	0.25
Physical Function	0.72	0.05	12.24	<0.0001
Week	0.17	0.08	2.100	0.036

R-sq.(adj) = 0.784 Deviance explained = 80.8%



Implications

- MVPA beneficial regardless of pre-existing conditions and other pain-related factors for better mood

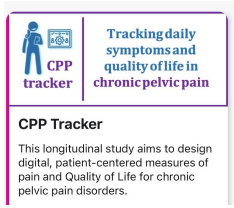


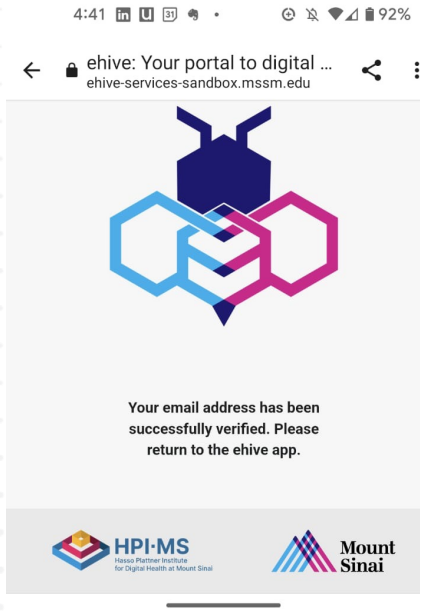
- Pain – PA relationship could be linear
- PSEQ – stable trait, more responsive to overall daily activity volume

Conclusion

- Complex interplay between health behaviors and symptom experience over time in CPPDs
  - –Likely similar to other chronic conditions
- Methods discussed here can be broadly applied to various research questions
- Similar conditions, data patterns, research questions







Thank you

- Emily Leventhal, BS
- Nivedita Nukavarapu, PhD
- Jovita Rodrigues, MS
- Matteo Danieletto, PhD
- Kyle Landell, BS
- Samia Shahnawaz, MS
- Bryan Trichoche, BS
- Thomas Fuchs, Dr. Sc.
- Leslee Shaw, PhD
- Michal Elovitz, MD
- Noémie Elhadad, PhD
- Suzanne Bakken, PhD
- Emma Horan, BS
- Melissa Nieves, MA

Funding: NIH/NICHD (1R01HD108263)

Contact:

ipek.ensari@gmail.com

ipek.ensari@mssm.edu

www.ipekensari.com

https://www.hpims.org/labs/ipek-ensari-lab/

Study website: https://www.hpims.org/research-projects/cpp-tracker/

HPI·MS

Mount Sinai

Hasso Plattner Institute for Digital Health at Mount Sinai

COLUMBIA | COLUMBIA UNIVERSITY IRVING MEDICAL CENTER

The End





Hasso Plattner Institute for Digital Health at Mount Sinai