Applied and Collaborative Research at CSCC

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UNC GILLINGS SCHOOL OF GLOBAL PUBLIC HEALTH

Overview

- Background: CSCC Experience
- Dissertation Research
  - PrecISE: Post hoc subgroup analysis in clinical trials
  - RIVUR: Real data application
- HCHS/SOL Work
  - Temporal patterns of sedentary behavior
  - Retention of Hispanics/Latinos

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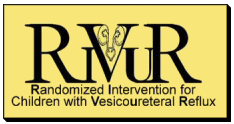
Background: CSCC Experience

Precision Interventions for Severe and/or Exacerbation-Prone Asthma Network (**PrecISE**)

- Developed statistical methods related to subgroup analysis

Hispanic Community Health Study / Study of Latinos (**HCHS/SOL**)

- Student Programmer during MS
- Graduate Research Assistant during PhD
- Developed statistical methods and manuals/guidelines
- Collaborated with investigators on manuscripts



Randomized Intervention for Children with Vesicoureteral Reflux (**RIVUR**)

- Used data as application examples

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Dissertation Research: **PrecISE**

- **PrecISE** is s a multi-arm multi-period crossover randomized clinical trial (RCT) in patients with severe asthma
- Investigating five novel therapies for patients with severe asthma
- Multiple endpoints
  - Forced expiratory volume in one second % predicted
  - 6-item Juniper Asthma Control Questionnaire score
  - CompEx events
- Goals
  - Assess the efficacy of each of the five interventions compared to placebo overall and in a biomarker-defined subgroup
  - Identify subgroups of patients with a large estimated treatment effect based on any of the 3 endpoints (or their combination)

PrecISE
PRECISION INTERVENTIONS FOR SEVERE ASTHMA

(Ivanova et al., 2020)

- Overall efficacy: favorable treatment effect in all patients at the end of RCT
- Discovery of patient subgroups with more pronounced responses than the overall population (perhaps even in absence of an overall effect), and identification of predictive baseline biomarkers
- Guideline-driven: Pre-specifies the subgroups
- Data-driven: Pre-specifies the subgroup selection strategy
    1) Define the targeted subgroups
    2) Estimate the subgroups from data
    3) Confirm the effects in estimated subgroups

(Lipkovich et al., 2023)

- Treatment indicator T (in a RCT, 0 = control, 1 = treatment)
- Candidate biomarkers $\mathbf{X}$
- The treatment effect in a subgroup S

$$\Delta(S) = E[Y^{(1)} - Y^{(0)} \mid \mathbf{X} \in S]$$

- Definitions of the "best" subgroup
  - All individuals with treatment effect > 0 (Imai and Ratkovic, 2013)
  - All individuals with treatment effect > δ (Foster et al., 2011)
- Existing definitions consider only one outcome
- Motivated by PrecISE, which has three endpoints of different types
- Need a definition for the best subgroup to consider
  - Multiple outcomes; specifically, outcomes of different types
  - Both the treatment effect and the size (maximize efficacy)

- For a single outcome, define the best subgroup as the one that maximizes a utility over all possible subgroups (Lai et al., 2014)

$$S_{true} = \arg\max_{S} U(S)$$

- We extend this definition to the case of multiple $J > 1$ outcomes

$$U(S, \boldsymbol{w}) = w_1 U_1(S) + \ldots + w_J U_J(S),$$

where

$$\boldsymbol{w} = (w_1, \ldots, w_J)$$

such that

$$\sum_{j=1}^{J} w_j^2 = 1$$

- Allows for a trade-off between the subgroup size and the treatment effect in the subgroup with respect to each outcome
- Optimal weights are typically not known in advance
- Estimate weights and the best subgroup from data simultaneously

Dissertation Research: **PrecISE**

- Consider continuous, binary, and censored time-to-event outcomes
- Adapt the penalized regression method to estimate best subgroups
- Simulation study
  - Sample size of 400 (200 in each arm)
  - Considered 4 independent uniform biomarkers and three correlated outcomes (continuous, binary, and censored-time-to-event)
  - Compared estimated weights vs. optimal weights
  - Similar estimation accuracy
  - Feasible to estimate weights and subgroup together
- Applicable to a multi-stage randomized clinical trial with prospective enrichment

Dissertation Research: **RIVUR**

- RCT (N = 607) aimed to determine whether long-term antimicrobial prophylaxis is effective, in children with vesicoureteral reflux, to prevent:
  - Primary outcome: Urinary tract infection (UTI) recurrence
  - Secondary outcome: Renal scarring
- Use of long-term antimicrobial prophylaxis treatment may lead to the development of antibiotic resistance and alterations of microbiome
- Number needed to treat (NNT) observed in the trial was large (10)
- Interest in identifying smaller and higher-risk subgroups of children that would benefit the most from long-term treatment

RIVUR
Randomized Intervention for Children with Vesicoureteral Reflux

(Hoberman et al., 2014)

- Estimated best subgroup in the RIVUR trial from 1 or 2 outcomes with the proposed utility-based definition and estimated weights

Outcomes	Size	UTI recurrence		Renal scarring	
		Risk difference (NNT)	p-value	Risk difference (NNT)	p-value
UTI & Renal scarring	85	0.24 (5)	0.02	0.006 (167)	0.95
UTI	427	0.10 (10)	0.01	0.01 (100)	0.72

- Proposed definition allowed incorporating the information from renal scarring into that of UTI recurrence to identify a subgroup with significantly larger clinical benefit (NNT = 5) from long-term antimicrobial prophylaxis than just using UTI recurrence (NNT = 10)

Dissertation Research: **RIVUR** and **PrecISE**

- PrecISE motivated work (submitted)

  Zhao, B., Fine, J., Ivanova, A.(2023). Finding the best subgroup with differential treatment effect with multiple outcomes. Submitted to Statistics in Medicine.

- More RIVUR application (in review)

  Zhao, B., Ivanova, A., Shaikh, N. (2023). Antimicrobial prophylaxis for vesicoureteral reflux: which subgroups of children benefit the most?. Research square, rs.3.rs-3286108. https://doi.org/10.21203/rs.3.rs-3286108/v1

- Subgroup confirmation work (published)

  Zhao, B., Ivanova, A., Fine, J. (2023). Inference on subgroups identified based on a heterogeneous treatment effect in a post hoc analysis of a clinical trial. *Clinical Trials*, *20*(4), 370-379. https://doi.org/10.1177/17407745231173055

Overview

- Background: CSCC Experience
- Dissertation Research
  - PrecISE: Post hoc subgroup analysis in clinical trials
  - RIVUR: Real data application
- **HCHS/SOL Work**
  - **Temporal patterns of sedentary behavior**
  - **Retention of Hispanics/Latinos**

Zhao, B., Sotres-Alvarez, D., Evenson, K.R., Greenlee, H., Mossavar-Rahmani, Y., Qi, Q., Marquez, D.X., Vidot, D.C., Elfassy, T., et al., 9900. **Day-of-the-Week and Time-of-the-Day Patterns of Sedentary Behavior** in the Hispanic Community Health Study / Study of Latinos. Medicine & Science in Sports & Exercise.

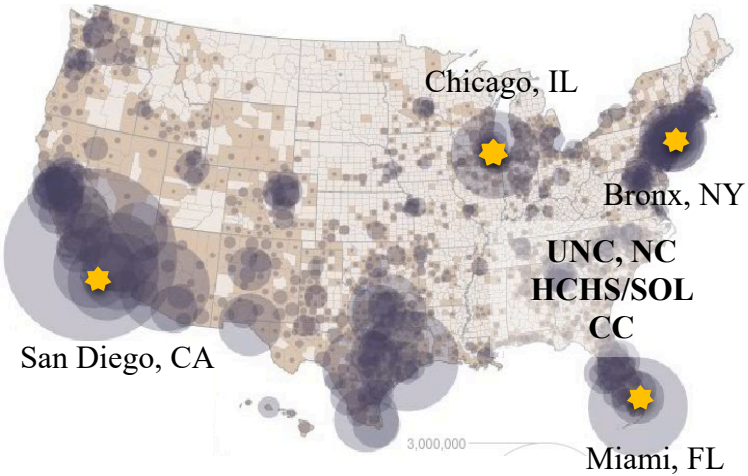
Moderated poster abstract presentation, AHA EPI 2023.

Perreira, K.M., Abreu, M.D.L.A., **Zhao, B.**, Youngblood, M.E., Alvarado, C., Cobo, N., Crespo-Figueroa, M., Garcia, M.L., Giachello, A.L., et al., 2020. **Retaining Hispanics**: Lessons From the Hispanic Community Health Study/Study of Latinos. American Journal of Epidemiology 189:518-31.

"**Multilevel Modelling** for Analyzing Correlated Data with Complex Sampling Design in HCHS/SOL". https://sites.cscc.unc.edu/hchs/node/12075

HCHS/SOL **Analysis Methods – Visit 2**. https://sites.cscc.unc.edu/hchs/node/6113

- **HCHS/SOL** is a multi-center, community-based cohort study (N = 16,415 US Hispanic/Latino adults, 18-74 yrs) at four urban field centers (Baseline, 2008-2011)
- Selected through a stratified multi-stage area probability sample design (Lavange et al., 2010)



Pew Hispanic Center (www.pewhispanic.org)

- Time spent in sedentary behavior is associated with incident cardiovascular disease (CVD)
- Conventional interventions to reduce sedentary behavior with a full-day approach have achieved mixed results
- An alternative strategy may be to target specific periods during the day and/or the week
- The goal is to examine **day-of-the-week** and **time-of-the-day** temporal patterns of sedentary behavior among U.S. Hispanic/Latino adults, overall and by sociodemographic characteristics

- Physical Activity
  - 1-week accelerometer (counts/minute)
  - Non-wear time determined by Choi algorithm (Choi et al., 2011)
  - Adherence: ≥ 3 days with ≥ 10 hrs of wear time per day
- Participants were instructed to remove the accelerometer device during water activities and sleep periods, but they might not do so
- Accelerometer cannot differentiate sleep from sedentary behavior

- **Sedentary bout**
  - An interval of one or more consecutive minutes in which the accelerometer registered <100 counts/min (sedentary time)
- **Sedentary break**
  - An interval of one or more consecutive minutes in which the accelerometer registered ≥ 100 counts/min (active time), between two sedentary bouts
- Non-wear time were not included in any bout or break
- Measures of sedentary behavior:
  - Total volume of sedentary time (mins/day)
  - Total volume of time in sedentary bouts ≥ 60 mins (mins/day)
  - Total number of sedentary breaks (/day)

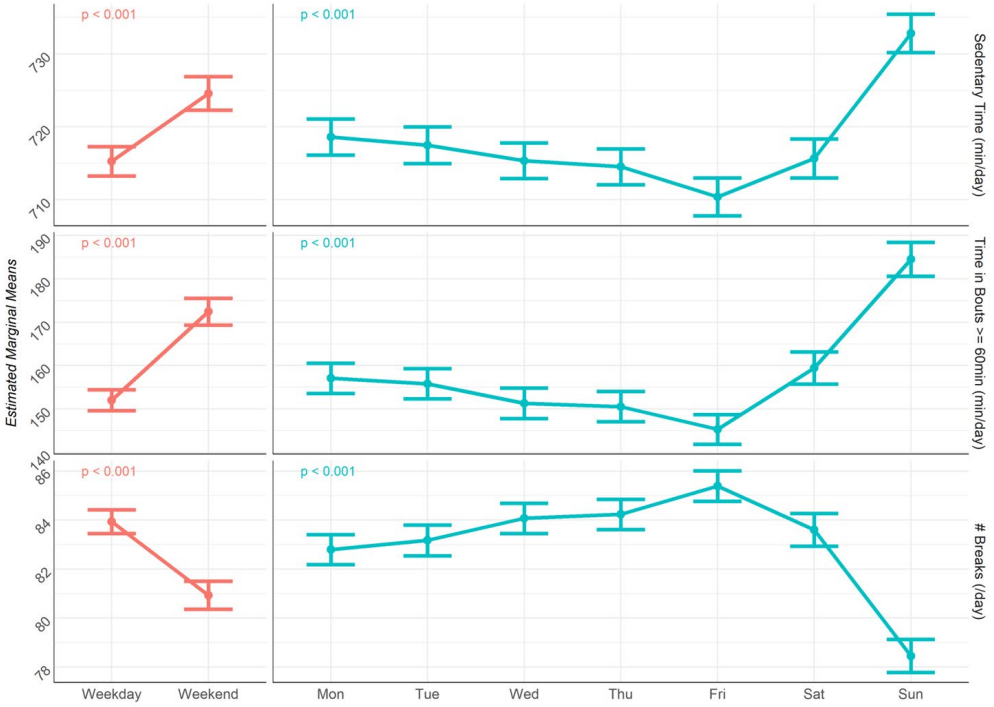
- **Day-of-the-week**
  - Analyzed by days of week
  - Summarized into weekday/weekend
- **Time-of-the-day**
  - Analyzed by 3-hr periods
  - Summarized into 6-hr periods
- Only considered data from adherent days (≥ 10 hrs of wear)
- Excluded excessive wear time (> 23hrs) and device malfunction (Moore et al., 2023)
- Final analytic sample size N = 12,241

- Multivariate-adjusted multi-level mixed-effects linear regression
  - Adjusted for sex, age group, field center, Hispanic/Latino background, employment, shift schedule, BMI (WHO), born in US, acculturation, education, income, season, moderate to vigorous physical activity, Short-Form 12 Health Survey mental and physical score, and wear time
  - Survey designs
    - Multi-level stratified and weighted pseudolikelihood
    - PSU-level (block groups) stratification
    - Actical multi-level inverse probability weighting (IPW) weights, accounting for complex survey design and missing Actical data
  - Random intercepts (households, participants) for clustering effect
  - Interaction between wear time and cross-classification of field center and Hispanic/Latino background

- Tested the significant interaction between time periods and each of the nine subgroups in separate models respectively
- Stratified analysis
  - By age, employment-shift, acculturation, field center, season

- Sensitivity analyses
  - Participants with at least one weekend day (N = 10,837)
  - Removing the 0:00 to 6:00 time period (N = 12,241)
  - Simultaneously account for weekend non-wear and wear during sleep, including only participants with at least one weekend and removing data from the 0:00 – 6:00 time period (N = 10,837)

- Sedentary behavior metrics by day of the week



- Sedentary behavior metrics by time of the day

- Discussion
  - Statistically significant variations in temporal patterns across day-of-the-week and time-of-the-day time periods for all three metrics
  - More sedentary on weekends than on weekdays, and most sedentary on Sundays
  - U-curve pattern, most sedentary late at night, less sedentary throughout the day, reached peak physical activity around noon, gradually more sedentary into the evening
  - Patterns were largely robust across seasonality and most sociodemographic characteristics

- Conclusion
  - Early mornings, evenings, weekends - the more sedentary periods- present windows of opportunity to reduce sedentary time

HCHS/SOL

- Examined the retention of Hispanics/Latinos in HCHS/SOL
- Across 5 years (2009 – 2016), HCHS/SOL maintained high contact, response, and participation rates
- The most difficult Hispanic/Latino populations to retain included young, single, US-born males with less than a high school education
- HCHS/SOL participants primarily sought to help their community and learn more about their health

Field Center and Response Status	Follow-up Interview											
	AFU1		AFU2		AFU3		AFU4		AFU5		Overall (AFUs 1–5)	
	No. of Persons	%	No. of Persons	%	No. of Persons	%	No. of Persons	%	No. of Persons	%	No. of Persons	%
Overall	16,197		16,135		16,067		16,009		15,930		15,930	
Contacted		96.5		95.0		93.4		91.3		89.8		83.3
Responded		95.5		94.3		92.7		90.3		88.6		81.3
Participated		87.9		87.2		84.4		82.2		81.1		67.2

- HCHS/SOL Analysis Methods - Visit 2
  - Provided data analytic guidelines to all HCHS/SOL investigators
  - Created multilevel sampling weights
  - Updated complex survey procedures and model-based procedures
  - Added multilevel modelling section
  - Contributed heavily to survival analysis section
  - Provided examples codes in 4 programming languages (SAS/SUDAAN, R, Stata, Mplus)
- Ongoing
  - Interval-censored survival analysis
  - Inverse sampling
  - Visit 3 variable definitions
  - …

Acknowledgement

- SPECIAL thanks to PrecISE Study PI, and my Dissertation Adviser: Anastasia Ivanova

- All co-authors
- HCHS/SOL Supervisor: Daniela Sotres-Alvarez
- HCHS/SOL Study PI: Jianwen Cai
- Staff and participants of HCHS/SOL

- Funding from National Heart, Lung, and Blood Institute (NHLBI)

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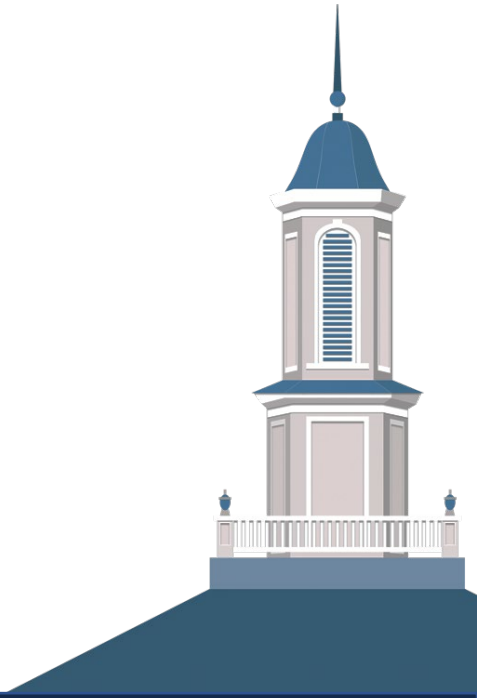
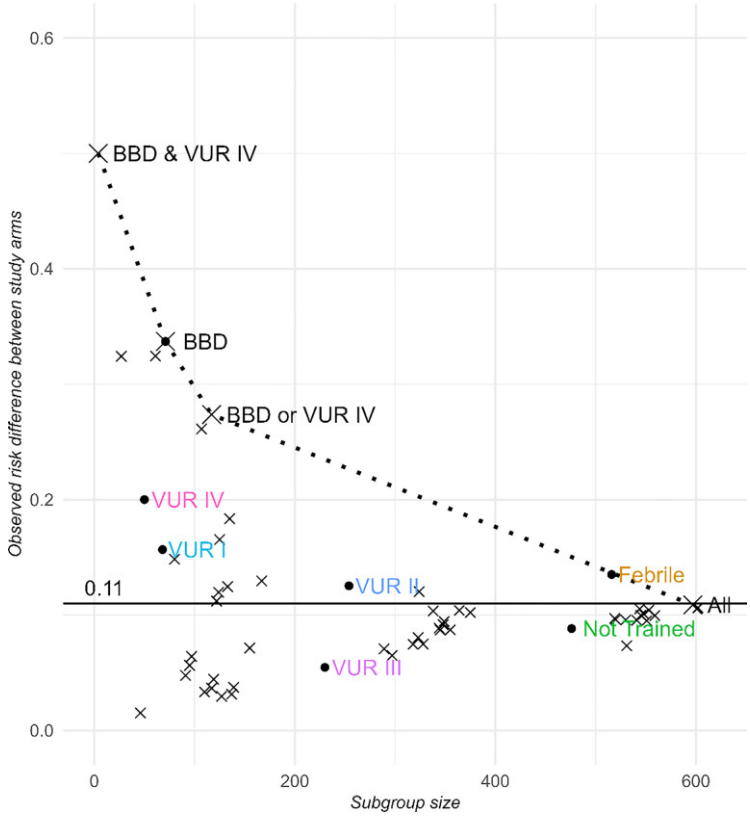
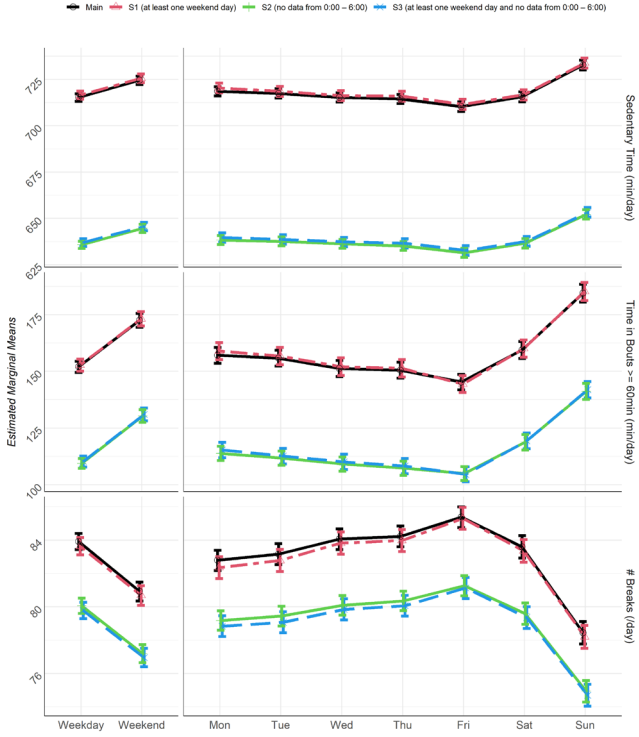
Thank You

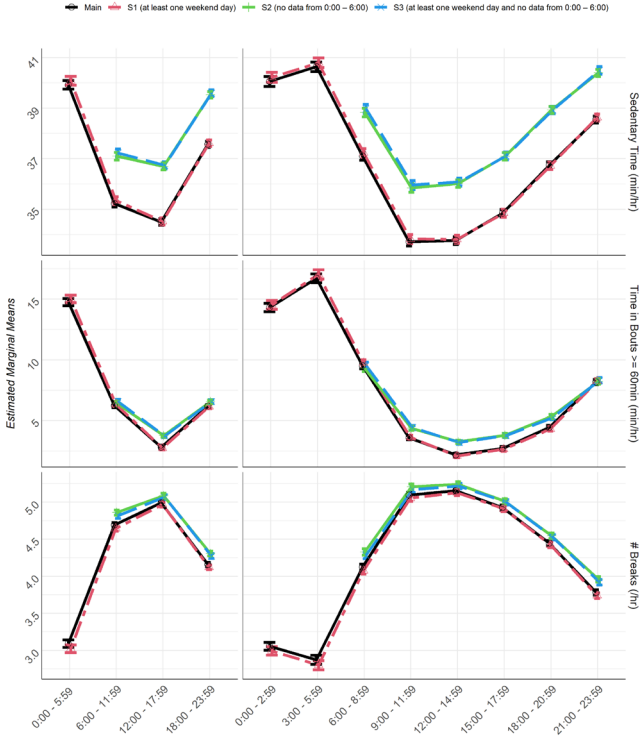


More RIVUR


0.6
0.4
0.2
0.0
Observed risk difference between study arms
BBD & VUR IV
BBD
BBD or VUR IV
VUR IV
VUR I
0.11
VUR II
Febrile
All
Not Trained
VUR III
0
200
400
600
Subgroup size

- Sensitivity Analyses





Collaborative Research at CSCC: HCHS/SOL

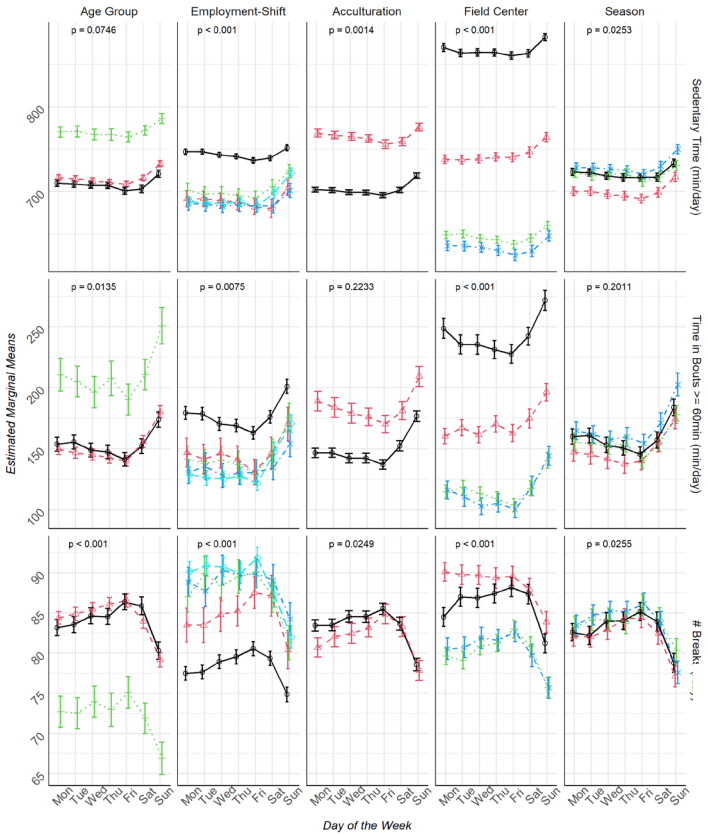


Figure 3. Estimated marginal means per day (95% CI) in sedentary behavior metrics by day of the week, stratified by subgroups, HCHS/SOL 2008-2011 (N = 12,241)

- Day-shift workers exhibited a sizeable uptick in sedentary time from Friday to Saturday while others did not show much change
- Chicago site exhibited an opposite trend for all sedentary metrics during weekdays comparing to other field centers

Collaborative Research at CSCC: HCHS/SOL

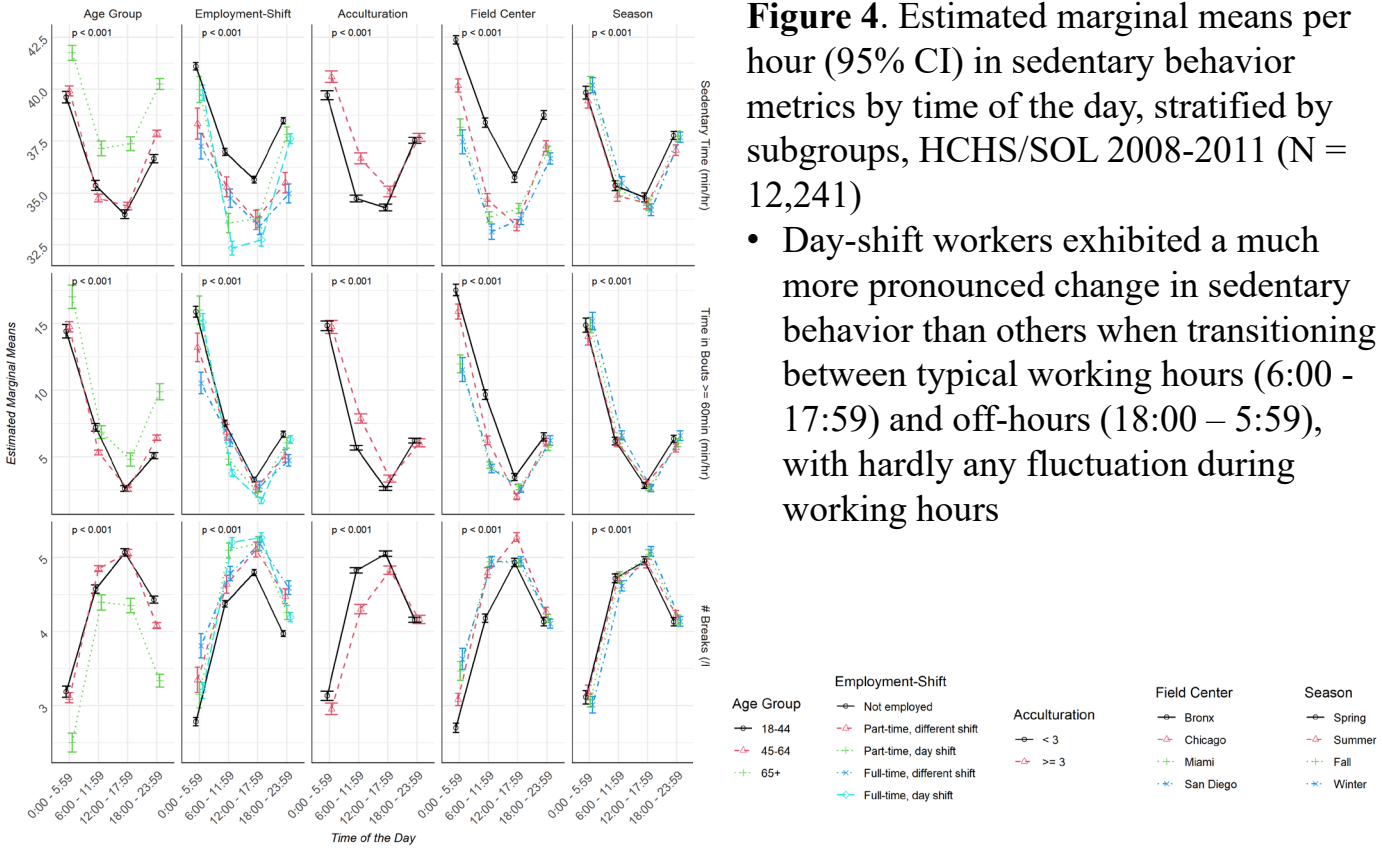


Figure 4. Estimated marginal means per hour (95% CI) in sedentary behavior metrics by time of the day, stratified by subgroups, HCHS/SOL 2008-2011 (N = 12,241)

- Day-shift workers exhibited a much more pronounced change in sedentary behavior than others when transitioning between typical working hours (6:00 - 17:59) and off-hours (18:00 – 5:59), with hardly any fluctuation during working hours