LONGITUDINAL STUDY OF THE IMPACT OF EXERCISE ON PROMIS®-BASED COGNITIVE OUTCOMES FOR PATIENTS IN THE MICHIGAN PREDICTIVE ACTIVITY AND CLINICAL TRAJECTORIES (MIPACT) STUDY

ABSTRACT

The MIPACT study represents a unique opportunity for researchers to garner insights from a conjunction of electronic health records, genomic information and wearable device-based data to improve scientific understanding of various physical and mental health issues. In this report we investigate the association between self-reported PROMIS® cognitive functioning scores and time spent exercising in the MIPACT participant cohort. Using a linear mixed model to fit the data while controlling for variability due to age, sex, race and marital status, we report a negative effect size of -0.021×10^{-2} (p-value: 0.004) for Exercise Time (in minutes) on self-reported PROMIS® scores, implying improved cognitive functioning. Some other associations of PROMIS® scores with race, sex and marital status are also noted.

1. INTRODUCTION

In recent years there has been a great deal of interest in patient-generated health data (Genes et al., 2018) collected from mobile apps and devices. In conjunction with electronic health records (EHR) and genomic data, data generated from mobile health apps represent exciting opportunities for the advancement of scientific understanding of the health issues and overall improvement of quality of life of patients.

The Michigan Predictive Activity and Clinical Trajectories (University of Michigan, 2017) (abbr. MIPACT) is one such prospective cohort study designed to integrate multiple sources of digital

data to better understand clinical phenotypes. Participants (recruited from the University of Michigan Hospital System) consented to provide access to parts of their electronic health record and to provide a blood sample for laboratory and genetic analyses. The study was funded in part by Apple, Inc and performed in partnership with Michigan Medicine. In addition to EHR data and blood draw-based data, patients were provided with an Apple Watch to track and collect data on their health and fitness. Further, patients were asked to complete quarterly surveys in which they were asked to report on their cognitive functioning in the week leading up to said survey.

The National Institutes of Health-funded Patient Reported Outcomes Measurement Information System (abbr. PROMIS®) is a publicly available short self-report form used to assess an individual's perception of their cognitive status. The form has two components – Cognitive Abilities and Cognitive Concerns. The former targets positive self-assessment such as "*my memory has been good as usual*" and "*I have been able to concentrate*" while the latter contains negatively worded questions which express concerns like "*my thinking has been slow*" and "*I have had trouble shifting back and forth between different activities that require thinking*". Items on both subscales use a 5-point rating from "*not at all*" to "*very much*". Items are summed to create a total score for each subscale (Becker et al., 2014; Valentine et al., 2019). The MIPACT study survey focuses on four Cognitive Concern-based questions, yielding a composite PROMIS® score that can vary between four and twenty.

There have been multiple studies which examine the anti-depressive effects of exercise. A comprehensive meta-analysis of fifty eight randomised trials examining the effects of exercise on depression revealed that participants in the exercise treatment arm had significantly lower depression scores than those receiving the control treatment, with an overall effect size of -0.80 (95% CI: [-0.92, -0.67]) (Rethorst et al., 2009). While there have been studies on the longitudinal

association between self-reported physical activity and anxiety and depression symptom severity for patients with Type 2 Diabetes and long-term physical disabilities(Battalio et al., 2020; Ivanova et al., 2017), there is a scarcity of population-level information on the effect of exercise on mental health. Using EHR data, patient survey data and Apple Watch-recorded activity, we aim to investigate the significance of the association between physical exercise and user-reported PROMIS® cognitive outcomes in patients enrolled in the MIPACT study.

2. METHODS

2.1. Study design and data collection

The MIPACT Study is a University of Michigan research study that aims to understand the relationship between biosensors, health information, and health outcomes. Participants were recruited from Michigan Medicine and surrounding communities and provided with an Apple Watch and an Omron Evolv Wireless Blood Pressure Monitor. Participants consented to provide access to parts of their EHR data and to provide a blood sample for laboratory and genetic analyses. In addition to a survey at time of entry in the study cohort, patients are asked to respond to quarterly surveys, which together serve as the source of self-reported PROMIS® scores for participants.

The Apple Watch and Health app provide information on normative heart rate, blood pressure, step count, and distance walking/running for these participants. One summary of physical activity called Apple Exercise Time measures every full minute of movement that equals or exceeds the intensity of a brisk walk. Apple watch automatically records exercise time. By default, the watch uses the accelerometer to estimate the intensity of the user's movement. However, during workout sessions, the watch uses additional sensors, like the heart rate sensor and GPS, to

generate estimates. Leveraging demographic information (such as age, sex, race and marital status) of participants from EHR data, we construct a dataset of 6,555 patients with quarterly self-reported PROMIS® scores and exercise data. Since PROMIS® scores are based on cognitive functioning of patients in the week leading up to the survey, we consider the time spent exercising during that time-period alone, yielding a longitudinal dataset with time-varying PROMIS® scores serving as the response and Apple Exercise Time as the primary covariate of interest. We use information from patients enrolled in the study from 2017 until November 2020.

2.2. Exploratory data analysis

The demographic covariates we consider include age of participant at time of enrolment, sex, race and marital status. Descriptive statistics like mean, median, standard deviation and range of the response are calculated by stratifying the dataset by age groups (18-30, 30-45, 45-60 and 60+), race (African American, Asian, Caucasian or other), sex (male or female) and marital status (unmarried or married). *Table 1* presents an overview of said descriptive statistics. *Figures 1, 2, 3* and *4* present smoothed time-varying curves of PROMIS® scores and corresponding Apple Exercise Time in MIPACT study participants when stratified by age group, race, sex and marital status respectively.

2.3. Statistical modeling of PROMIS® scores

A covariate-adjusted linear mixed model (LMM) is fit to the dataset. The response is self-reported PROMIS® summary score from intake and follow-up surveys and the primary covariate of interest is the Apple Exercise Time of each patient in the week leading up to each survey.

Additional covariates include age groups, sex, race and marital status. The LMM may be represented as follows

$$Y_{ij} = \beta_0 + b_i + \beta_1 AET_{ij} + \beta_2 I(S_i = Male) +$$

$$\beta_3 I(A_i = 30 - 45) + \beta_4 I(A_i = 45 - 60) + \beta_5 I(A_i = 60 +) +$$

$$\beta_6 I(R_i = \text{Asian}) + \beta_7 I(R_i = \text{Caucasian}) +$$

$$\beta_8 I(MS_i = \text{Unmarried}) + \sum_{k=1}^{10} \beta_{8+k} I(Time_{ij} = k) + \epsilon_{ij}$$

where Y_{ij} is the response of the ith participant during the jth survey. Since enrolment is a rolling process, the number of survey responses from an individual depends on how long they have been a part of this study cohort. As defined before, AET_{ij} is the Apple Exercise Time for the ith person in the week leading up to the jth survey. A_i, R_i, S_i and MS_i denote age at enrollment, race, sex and marital status of the ith participant. A person-specific random intercept $b_i \sim N(0, \sigma_b^2)$ is added to capture the within-subject correlation in the dataset, and an independent white noise term $\epsilon \sim N(0, \sigma_e^2)$ is included as well. We also include a categorical covariate to account for variation in the response across surveys (intake and subsequent follow-ups). The coefficients $\beta_9, \beta_{10}, \dots, \beta_{18}$ are the corresponding coefficients, with $k = 1, 2, \dots$ signifying the first intake survey, first quarterly survey and so on. Since there are a maximum of ten surveys (one intake and nine follow-ups), we have $1 \leq k \leq 10$. We note that although the response is a count-type variable, we still use a linear model to investigate the presence of any significant association between the response and covariate of interest. *Table 2* presents a summary of the model described above.

All analyses, preparation of tables and graphical devices were performed using R (R Core Team, 2014). Data was cleaned using the tidyverse and lubridate (Grolemund & Wickham, 2011;

Wickham et al., 2019) packages. All graphical devices were generated using the ggplot (Villanueva & Chen, 2019) package, while the LMM was fit using the lme4 (Bates et al., 2015, p. 4) package. The code used to clean and analyse the data may be found in the Github repository https://github.com/soumikp/bios629.

3. RESULTS

Table 1 presents an overview of how the self-reported PROMIS® scores vary when stratified by age group, sex, race and marital status. We do not note the presence of any major difference in group-stratified means over all time points, however *Figures 1, 2, 3* and *4* indicate the presence of appreciable between-group differences in PROMIS® scores when stratified by gender and marital status, in particular. This between-group disparity is less evident when stratifying by age group and race. We further note the presence of visible disparities in Apple HealthKit Exercise Time values when stratifying by age, race, sex and marital status.

Table 2 presents a summary of linear mixed model fit to examine association of self-reported PROMIS® scores with HealthKit-based Apple Exercise Time, while controlling for age, sex, race and marital status. A categorical time covariate is included given the unbalanced longitudinal nature of the data. We note a significant association between time spent exercising and self-reported PROMIS® scores with an effect size of -0.021×10^{-2} (p-value: 0.004). Specifically, for every additional 100 minutes spent exercising, the expected decrease in PROMIS® scores is -0.021, implying improved perception of cognitive functioning in study participants, controlling for other covariates in the model. Other significant associations include an effect size of -0.589 (p-value: < 0.001) for male participants as compare to (otherwise identical) female counterparts in the study, controlling for variation in all other covariates. A brief literature review did not yield

any satisfactory finding to support this conclusion. We note that these scores are self-reported and are reflective of participant-specific subjective perception of cognitive functioning and are not objective measures. Unmarried participants report significantly higher PROMIS® scores, indicating poorer cognitive functioning as compared to (otherwise identical) married participants, with an estimated effect size of 0.367 (p-value < 0.001). We also note that Asian participants report significantly better cognitive functioning as compared to the baseline group of African Americans in the study, with an effect size of -0.515 (p-value: < 0.001).

4. CONCLUSION

The MIPACT study represents a unique opportunity for remote patient monitoring and timely intervention to improve standards of care for patients. There is scope for researchers to garner insights from this study to improve scientific understanding of various physical and mental health issues. In this report we investigate the association between self-reported PROMIS® cognitive functioning scores and time spent exercising in the MIPACT participant cohort. Using an LMM to model the data while controlling for variability due to age, sex, race and marital status, we report a significant negative effect of Exercise Time (in minutes) on self-reported PROMIS® scores – this finding agrees with previous studies which noted improved cognitive functioning with increased physical activity (Hötting & Röder, 2013; Mandolesi et al., 2018).

Some other associations of PROMIS® scores with race and marital status are also noted. We note that Asian participants in this study are likely to report significantly better cognitive functioning as compared to African American participants. A caveat here is that our finding must be interpreted in light of the fact that race has an indirect effect on cognitive functioning through social risk factors like education and health insurance (Avila et al., 2019; Zsembik & Peek, 2001).

Unmarried people are expected to report higher PROMIS® scores implying poorer cognitive functioning as compared to otherwise identical married participants in this study, agreeing with findings from a recent longitudinal study which notes that marital status is a potentially important but overlooked social risk/protective factor for poor cognitive functioning (Liu et al., 2019).

REFERENCES

Avila, J. F., Vonk, J. M. J., Verney, S. P., Witkiewitz, K., Arce Rentería, M., Schupf, N., Mayeux, R., & Manly, J. J. (2019). Sex/gender differences in cognitive trajectories vary as a function of race/ethnicity. *Alzheimer's & Dementia*, *15*(12), 1516–1523. https://doi.org/10.1016/j.jalz.2019.04.006

Bates, D., Mächler, M., Bolker, B., & Walker, S. (2015). Fitting Linear Mixed-Effects Models Using **lme4**. *Journal of Statistical Software*, *67*(1). https://doi.org/10.18637/jss.v067.i01

Battalio, S. L., Huffman, S. E., & Jensen, M. P. (2020). Longitudinal associations between physical activity, anxiety, and depression in adults with long-term physical disabilities. *Health Psychology*, *39*(6), 529–538. https://doi.org/10.1037/hea0000848

Becker, H., Stuifbergen, A., Lee, H., & Kullberg, V. (2014). Reliability and Validity of PROMIS Cognitive Abilities and Cognitive Concerns Scales Among People with Multiple Sclerosis. *International Journal of MS Care*, *16*(1), 1–8. https://doi.org/10.7224/1537-2073.2012-047

Genes, N., Violante, S., Cetrangol, C., Rogers, L., Schadt, E. E., & Chan, Y.-F. Y. (2018). From smartphone to EHR: A case report on integrating patient-generated health data. *Npj Digital Medicine*, *1*(1), 23. https://doi.org/10.1038/s41746-018-0030-8

Grolemund, G., & Wickham, H. (2011). Dates and Times Made Easy with **lubridate**. *Journal of Statistical Software*, *40*(3). https://doi.org/10.18637/jss.v040.i03

Hötting, K., & Röder, B. (2013). Beneficial effects of physical exercise on neuroplasticity and cognition. *Neuroscience & Biobehavioral Reviews*, *37*(9), 2243–2257. https://doi.org/10.1016/j.neubiorev.2013.04.005

Ivanova, E., Burns, R. J., Deschênes, S. S., Knäuper, B., & Schmitz, N. (2017). A Longitudinal Investigation of Anxiety and Depressive Symptomatology and Exercise Behaviour Among Adults With Type 2 Diabetes Mellitus. *Canadian Journal of Diabetes*, *41*(1), 73–81. https://doi.org/10.1016/j.jcjd.2016.07.006

Liu, H., Zhang, Y., Burgard, S. A., & Needham, B. L. (2019). Marital status and cognitive impairment in the United States: Evidence from the National Health and Aging Trends Study. *Annals of Epidemiology*, *38*, 28-34.e2. https://doi.org/10.1016/j.annepidem.2019.08.007

Mandolesi, L., Polverino, A., Montuori, S., Foti, F., Ferraioli, G., Sorrentino, P., & Sorrentino, G. (2018). Effects of Physical Exercise on Cognitive Functioning and Wellbeing: Biological and Psychological Benefits. *Frontiers in Psychology*, *9*, 509. https://doi.org/10.3389/fpsyg.2018.00509

Rethorst, C. D., Wipfli, B. M., & Landers, D. M. (2009). The Antidepressive Effects of Exercise: A Meta-Analysis of Randomized Trials. *Sports Medicine*, *39*(6), 491–511. https://doi.org/10.2165/00007256-200939060-00004

University of Michigan. (2017). *Michigan Predictive Activity and Clinical Trajectories (MIPACT) Study*. MIPACT | University of Michigan. https://precisionhealth.umich.edu/our-research/mipact/

Valentine, T. R., Weiss, D. M., Jones, J. A., & Andersen, B. L. (2019). Construct validity of PROMIS® Cognitive Function in cancer patients and noncancer controls. *Health Psychology*, *38*(5), 351–358. https://doi.org/10.1037/hea0000693

Villanueva, R. A. M., & Chen, Z. J. (2019). ggplot2: Elegant Graphics for Data Analysis (2nd ed.). *Measurement: Interdisciplinary Research and Perspectives*, *17*(3), 160–167. https://doi.org/10.1080/15366367.2019.1565254

Wickham, H., Averick, M., Bryan, J., Chang, W., McGowan, L., François, R., Grolemund, G., Hayes, A., Henry, L., Hester, J., Kuhn, M., Pedersen, T., Miller, E., Bache, S., Müller, K., Ooms, J., Robinson, D., Seidel, D., Spinu, V., … Yutani, H. (2019). Welcome to the Tidyverse. *Journal of Open Source Software*, *4*(43), 1686. https://doi.org/10.21105/joss.01686

Zsembik, B. A., & Peek, M. K. (2001). Race Differences in Cognitive Functioning Among Older Adults. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *56*(5), S266–S274. https://doi.org/10.1093/geronb/56.5.S266

Covariate	PROMIS® scores		
	Mean (SD)	Median [Min, Max]	Missing (%)
Overall (N = 6555)	6.83 (3.37)	6.00 [4.00, 20.00]	22 (0.3%)
Age group (in years)			
18 – 30 (N = 1445)	6.68 (3.32)	5 [4, 20]	5 (0.3%)
30 – 45 (N = 1510)	6.89 (3.55)	6 [4, 20]	4 (0.3%)
45 – 60 (N = 1878)	6.81 (3.41)	6 [4, 20]	9 (0.5%)
60 + (N = 1709)	6.87 (3.21)	6 [4, 20]	4 (0.2%)
Race			
African American (N = 1115)	7.06 (3.54)	6 [4, 20]	11 (1.0%)
Asian (N = 1040)	6.38 (2.92)	5 [4, 20]	3 (0.3%)
Caucasian (N = 3640)	6.89 (3.41)	6 [4, 20]	7 (0.2%)
Other (N = 760)	6.85 (3.48)	6 [4, 20]	1 (0.1%)
Sex			
Female (N = 3521)	7.11 (3.51)	6 [4, 20]	10 (0.3%)
Male (N = 3034)	6.48 (3.15)	5 [4, 20]	12 (0.4%)
Marital Status			
Married (N = 3629)	6.70 (3.25)	6 [4, 20]	13 (0.4%)
Unmarried (N = 2367)	7.00 (3.55)	6 [4, 20]	9 (0.4%)

Table 1: *Descriptive summary of PROMIS® scores when stratified by age, sex, race and marital status.*
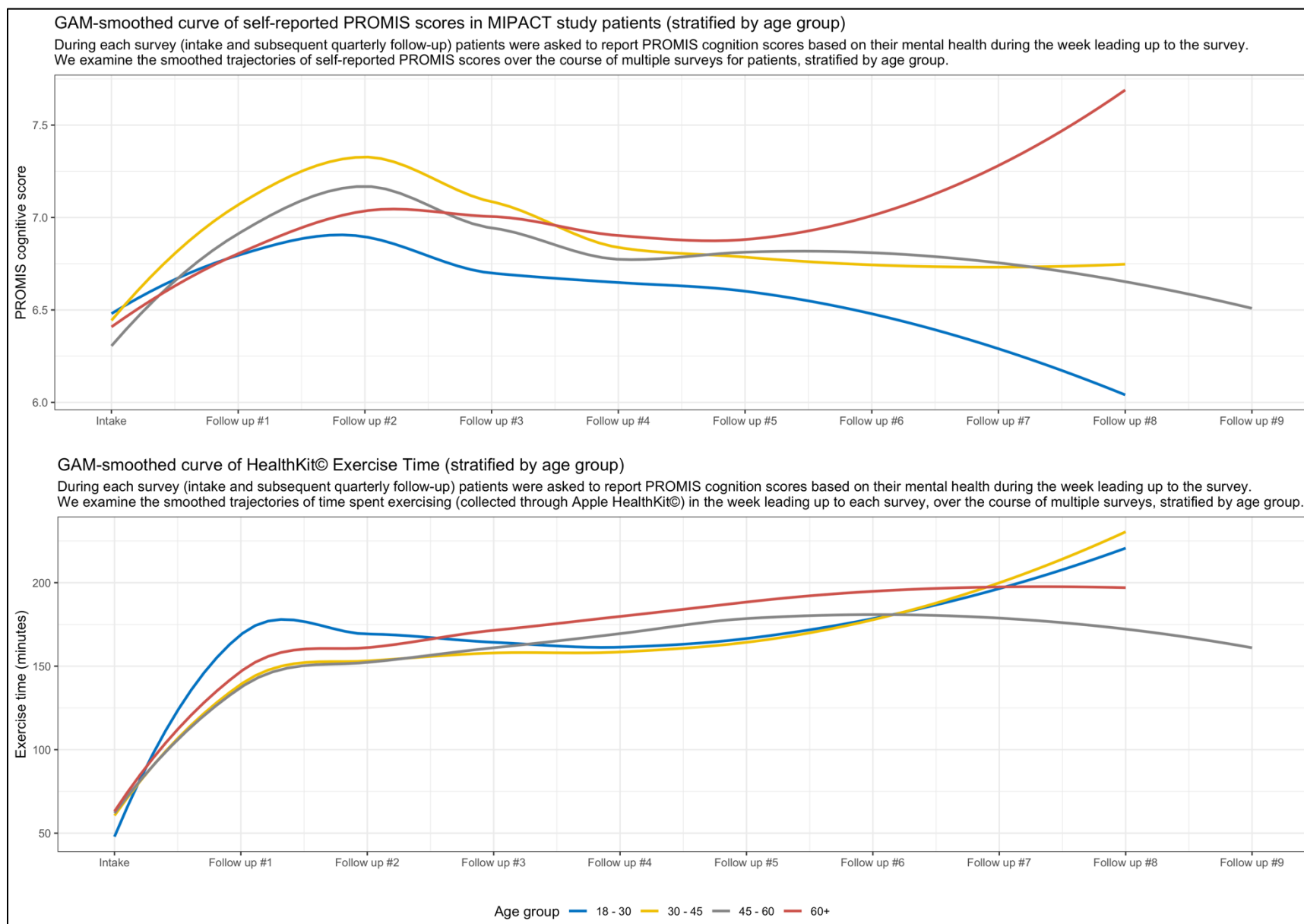
Figure 1: *Smoothed curve of time-varying self-reported PROMIS® scores and HealthKit Exercise Time when stratified by age groups.*
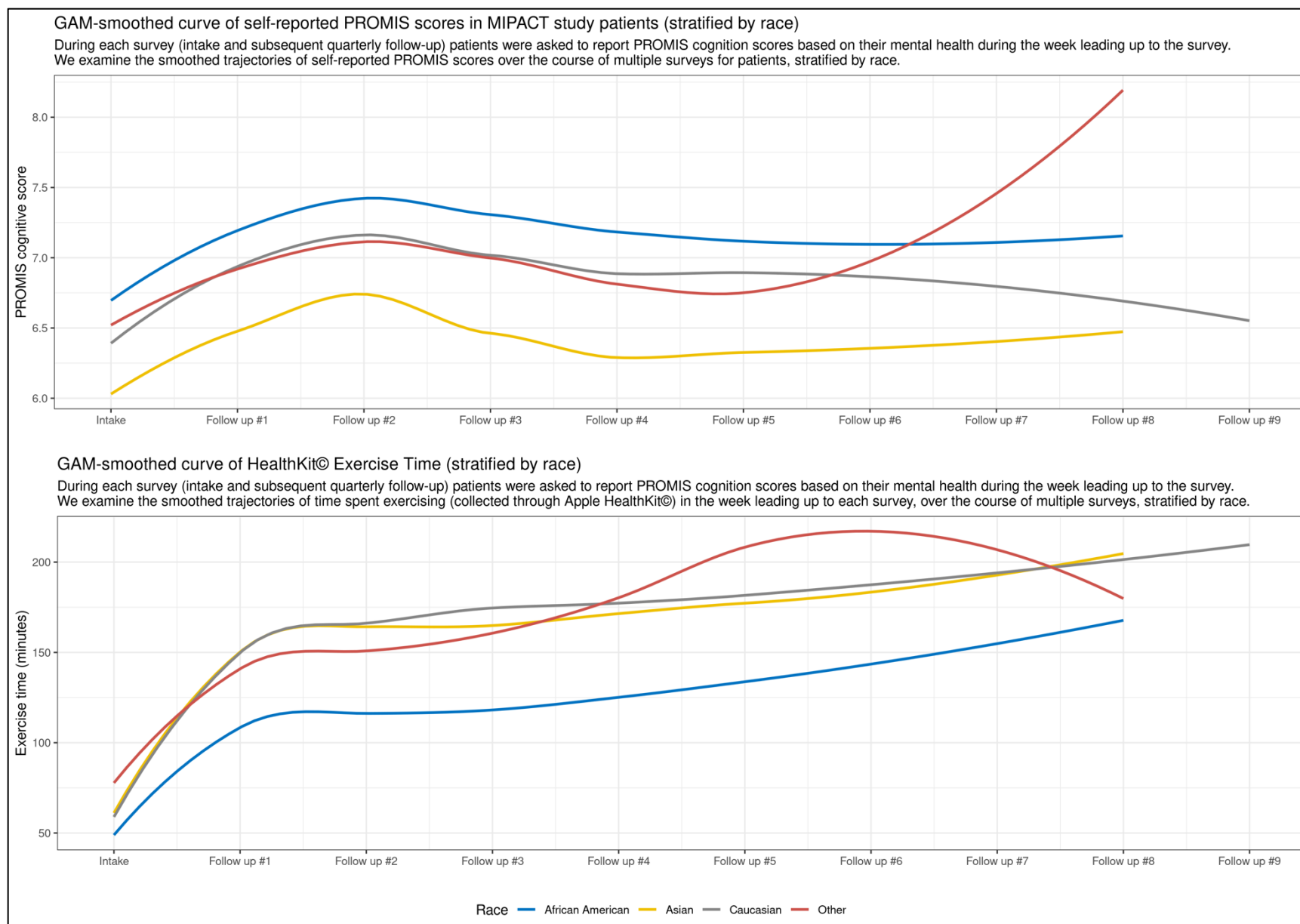
Figure 2: *Smoothed curve of time-varying self-reported PROMIS® scores and HealthKit Exercise Time when stratified by race.*
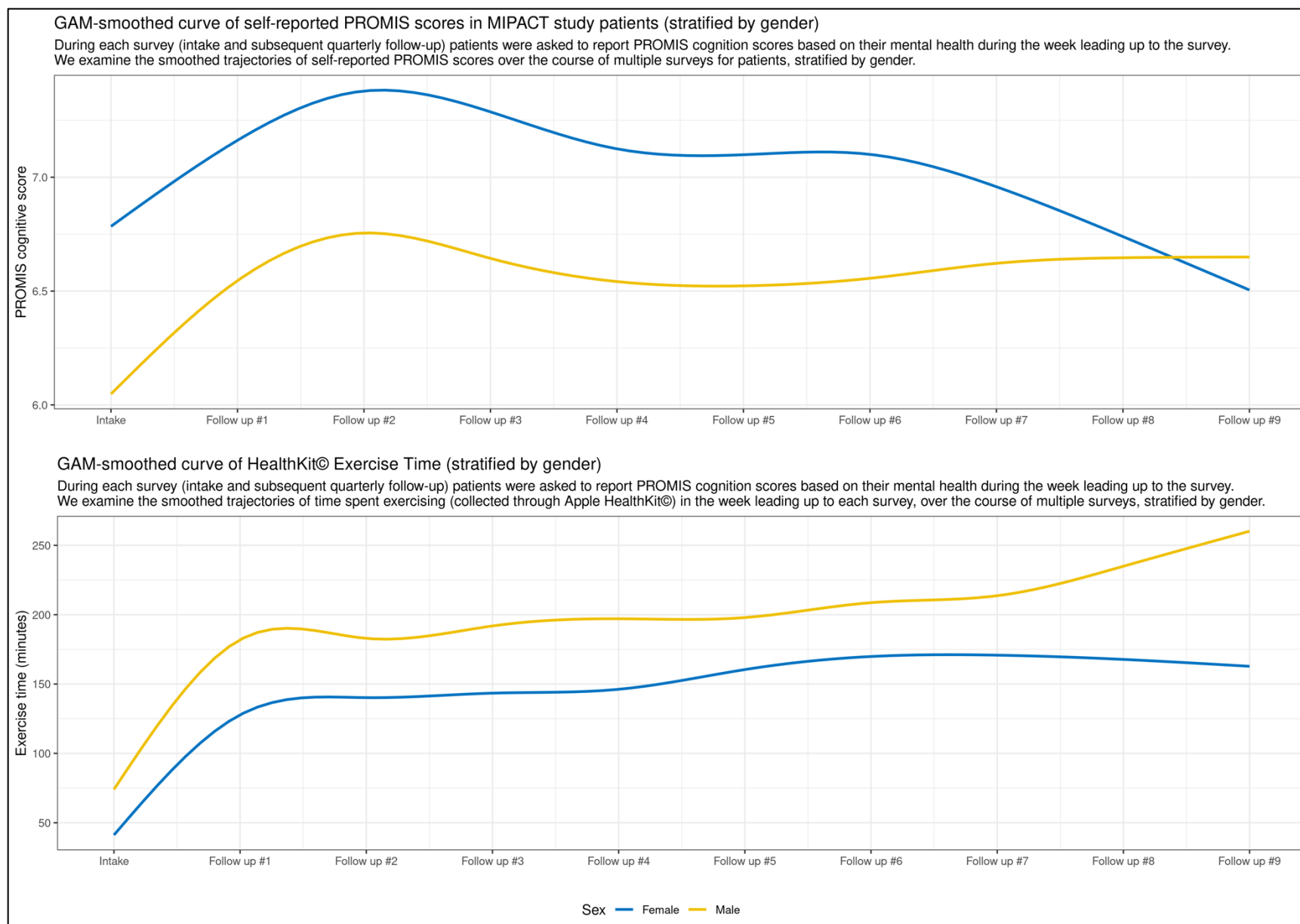
Figure 3: *Smoothed curve of time-varying self-reported PROMIS® scores and HealthKit Exercise Time when stratified by sex.*
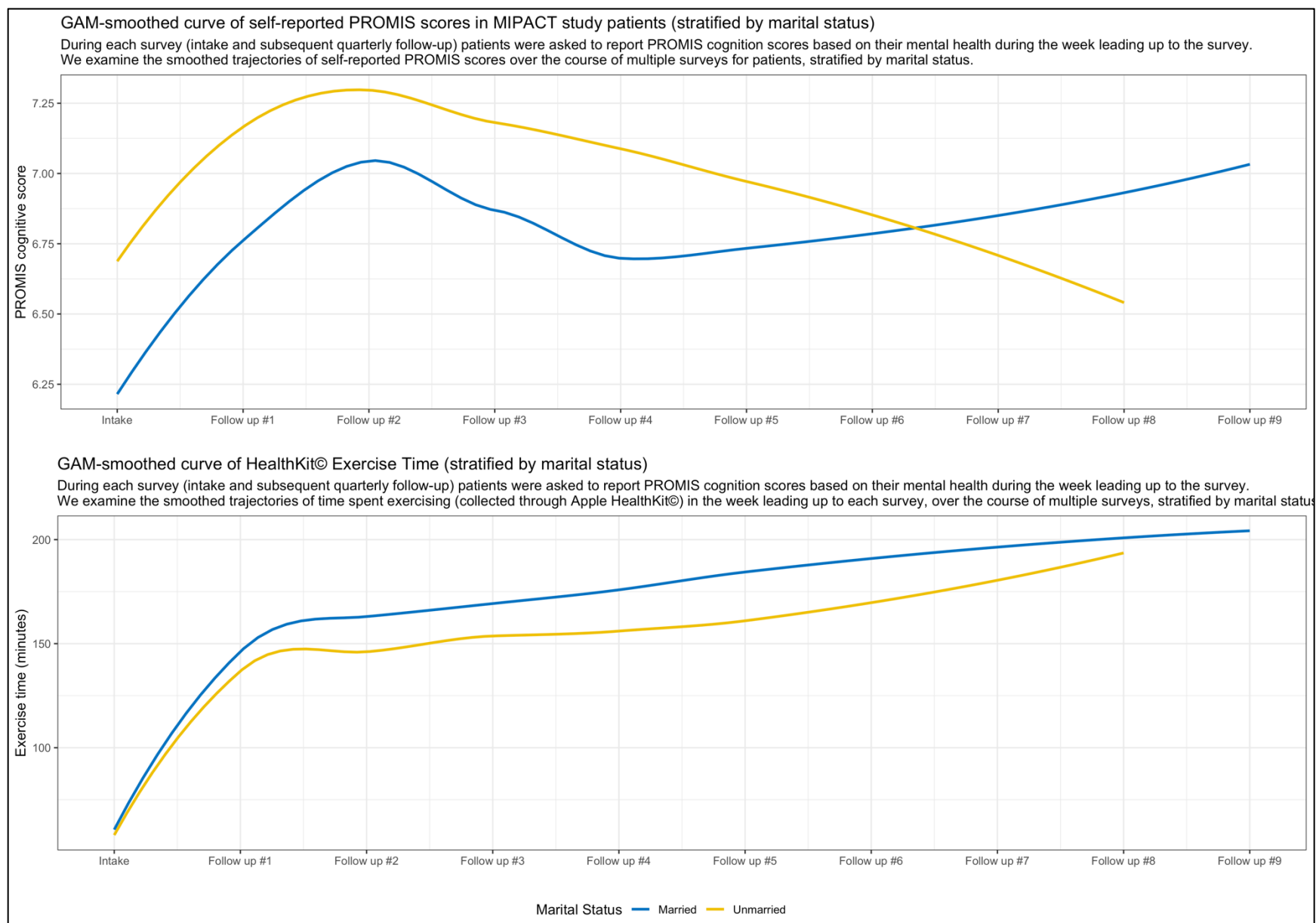
Figure 4: *Smoothed curve of time-varying self-reported PROMIS® scores and HealthKit Exercise Time when stratified by marital status.*

Fixed effects			
Predictors	**Estimate**	**Std. Error**	**t-value**
Intercept	*6.615*	*0.185*	*35.794**
Time (Baseline = Intake)	-	-	-
Quarterly follow-up 1	*0.535*	*0.040*	*13.271**
Quarterly follow-up 2	*0.839*	*0.042*	*20.054**
Quarterly follow-up 3	*0.679*	*0.043*	*15.692**
Quarterly follow-up 4	*0.586*	*0.045*	*12.953**
Quarterly follow-up 5	*0.663*	*0.050*	*13.237**
Quarterly follow-up 6	*0.874*	*0.060*	*14.533**
Quarterly follow-up 7	*0.798*	*0.092*	*8.654**
Quarterly follow-up 8	*0.773*	*0.192*	*4.025**
Quarterly follow-up 9	1.589	1.429	1.112
Age	0.111×10^{-2}	0.275×10^{-2}	0.405
Sex (Baseline = Female)	-	-	-
Male	*-0.589*	*0.078*	*-7.537**
Marital Status (Baseline: Married)	-	-	-
Unmarried	*0.367*	*0.091*	*4.052**
Race (Baseline: African American)	-	-	-
Asian	*-0.515*	*0.139*	*-3.702**
Caucasian	-0.083	0.112	-0.745
Other	-0.041	0.155	-0.267
Apple Exercise Time	-0.021×10^{-2}	0.007×10^{-2}	*-2.885**
Random effects			
Groups	**Name**	**Variance**	**Std. Dev.**
Patient ID	Random intercept	7.562	2.750
Residual	White noise	3.693	1.922

Table 2: *Summary of linear mixed model fit to examine association of self-reported PROMIS® scores with HealthKit-based Apple Exercise Time, while controlling for age, sex, race and marital status. A categorical time covariate is included given the unbalanced longitudinal nature of the data. We note a significant association between time spent exercising and self-reported PROMIS® scores. A negative effect size is*

noted. Specifically, for every additional 100 minutes spent exercising, the expected decrease in PROMIS® scores is -0.021, implying improved perception of cognitive functioning in study participants, controlling for other covariates in the model. Other significant associations include a negative effect size of -0.589 for male participants as compare to their female counterparts in the study, controlling for variation in all other covariates. Unmarried participants report significantly higher PROMIS® scores, indicating poorer cognitive functioning as compared to (otherwise identical) married participants, with an estimated effect size of 0.367. Asian participants report significantly better cognitive functioning as compared to the baseline group of African Americans in the study, with an effect size of -0.515. All significant associations are italicised in the table above.