Title
Physical activity measurement in breast cancer survivors: Methodological issues, solutions, and applications

Author
Nelson, Sandahl Hygeia

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Physical Activity Measurement in Breast Cancer Survivors: Methodological Issues, Solutions, and Applications

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy

in

Public Health (Epidemiology)

by

Sandahl H. Nelson

Committee in Charge:

University of California San Diego

Professor Loki Natarajan, Co-Chair
Professor Ruth Patterson, Co-Chair
Professor Sheri Hartman

San Diego State University

Professor Caroline Thompson
Professor Eric Buhi-Walsh

2018

The Dissertation of Sandahl H. Nelson is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

Co-Chair

Co-Chair

University of California San Diego

San Diego State University

2018

DEDICATION

To my wonderful and supportive husband, Igor. Thank you for always pushing me to be my best.

EPIGRAPH

Physical activity. Think of it as a medication you need to take daily.

– Anonymous

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ACKNOWLEDGMENTS

I have been so fortunate to have many mentors and collaborators, so this list will be long and not all inclusive but to everyone I have worked with, know that I am so grateful. First, I would like to thank Dr. Ruth Patterson, not only did reading about her work provide the excitement and impetus to apply to the program, but her mentorship and guidance has helped me to succeed in it. Our weekly meetings kept me on track in my early years of the program, all of my papers are better because of the mark she put on them, and I know that I have become a 100-fold better writer than I ever would have been without her effort. I also thank her for the use of the RFH data, which would not exist without her vision and drive. Next, I would also like to thank Dr. Sheri Hartman for working with me daily and really teaching me the nitty gritty of research, from conception to final product my close work with her has helped me grow so much as a researcher. Even when mentoring me she treated me like a colleague, this respect gave me the confidence to excel and I will forever be grateful for it! Dr. Loki Natarajan also deserves a great debt of gratitude for being my statistical mentor, despite how busy she is, she always made time to meet. She let me run my analysis plans by her and helped me grow as a statistician both in knowledge and in confidence. She has a special knack for making you feel like there are no dumb questions. Thank you also to Dr. Jacqueline Kerr for bringing me into the world of physical activity research and spending the time conversing with me about it in a way that sparked me to come up with my own questions.

I would also like to thank Dr. Catherine Marinac (although the Dr. came later) she was an amazing office mate, the best possible role model for how to excel in a PhD program, and a great collaborator. She raised the bar and my work benefitted because of it! I would also like to thank Selene Xu for her help with the simulation in my second paper, Lauren Weiner for her work with the ACT study, Brian Kwan for his help when my Fitbit cleaning code exploded, and Suneeta Godbole for all her work cleaning accelerometer data.

While I could not have achieved this work without my mentors and colleagues I also could not have gotten here without my family. Thank you to my Father for always believing in me and pushing me academically. Thank you to my Mother for being a sounding board and for stepping up as a Grandma so that I could actually get work done. Thank you to my husband for always supporting me and pushing me to be my best, it may be a cliché to say it, but I really mean it, I am the best version of myself because you are in my life. Lastly, to my son who as I write this is 7 months old, thank you for being the best type of distraction yet increasing my ability to work efficiently, you put into perspective what is truly important.

Lastly, while there are so many people without whom this work could not have become reality, my deepest thanks go to the participants of the RFH and (in particular) the ACT study. These women were going through what was likely one of the hardest times of their lives, a new breast cancer diagnosis, yet they still found the time, energy, and altruism to participate in a study. A study that, while it would increase our understanding of activity to benefit future breast cancer patients, would have no direct benefit to them. Their selflessness is an example I hope to carry with me always.

Chapter 1 is currently in submission for the publication of the material. Co-authors include Dr. Loki Natarajan, Dr. Ruth Patterson, Dr. Sheri Hartman, Dr. Caroline Thompson, Suneeta Godbole, Eileen Johnson, Dr. Catherine Marinac, and Dr. Jacqueline Kerr. The dissertation author was the primary investigator and author of this material.

Chapter 2 is currently being prepared for submission for the publication of the material. Co-authors include Selene Xu, Suneeta Godbole, Dr. Ruth Patterson, Dr. Jacqueline Kerr, Dr.

Sheri Hartman, Dr. Caroline Thompson, and Dr. Loki Natarajan. The dissertation author was the primary investigator and author of this material.

Chapter 3 is currently being prepared for submission for the publication of the material. Co-authors include Lauren Weiner, Dr. Loki Natarajan, Dr. Barbara Parker, Dr. Ruth Patterson, and Dr. Sheri Hartman. The dissertation author was the primary investigator and author of this material.

VITA

EDUCATION

2018	Doctor of Philosophy in Public Health (Epidemiology). University of California San Diego / San Diego State University
2014	Master of Science, Biostatistics. University of California Los Angeles
2007	Master of Science, Biology. University of California San Diego
2005	Bachelor of Science in Physiology and Neuroscience. University of California San Diego

RESEARCH EXPERIENCE

09/2014-07/2018, Moores Cancer Center, UCSD: Graduate Student Biostatistician.

A research position in the department of cancer prevention and control at UCSD's Moores Cancer Center. Working as the biostatistician on numerous projects under the indirect supervision of a principle Biostatistician.

- Statistical analysis and data management of randomized trials for lifestyle interventions among breast cancer survivors
- Preparation of analytic plans
- Manuscript preparation and submissions

09/2013-09/2014, Center for Community Health (CCH) & Center for HIV Identification, Prevention, and Treatment Services (CHIPTS), UCLA: Graduate Student Biostatistician.

A research position in a group consisting of researchers of the Semel Institute's Center for Community Health and CHIPTS. Working as the biostatistician on numerous projects under the indirect supervision of a principle Biostatistician.

- Statistical analysis and data management of community health data using SAS
    - Longitudinal, mixed model, analysis of a large community intervention cohort study
    - Paired analysis in a youth depression/PTSD study
    - Non-parametric analysis of pilot study data
- Power/sample size calculations and writing of statistical sections for grants
- Writing of statistical sections of papers for publication submission

5/2013-9/2013: Los Angeles Veterans Administration, Home Based Primary Care: Student Statistician.

Working at the VA on a research grant for home based primary care (HBPC) that focused on the use of geospatial software to analyze the quality of care provided and maximize patient health (have continued on as a statistical consultant for the project).

- Statistical analysis of home-based primary care data using SAS
    - Analysis of:
        - Patient health outcomes correlated to practitioner travel distance
        - Emergency preparedness following a practitioner delivered intervention

        - Workforce efficiency following a geospatial mapping intervention
- Geospatial analysis and mapping of patients using ArcGIS
- Survey design and administration

3/2007-10/2008: Ferring Research Institute Inc: Research Associate II.

Working as a research associate at Ferring Pharmaceuticals a private, research-driven specialty biopharmaceutical company active in global markets.

- Designed and executed pre-clinical, *in-vivo* studies of various endocrine pharmaceuticals, including pharmaceuticals for osteoporosis, prostate cancer, and in vitro fertilization
- Prepared, statistically analyzed, and presented data from all experiments using excel and Prism
- Successfully developed and validated novel protocols for immunohistochemical assays

TEACHING ACTIVITIES

University of California San Diego

- Teaching Assistant and Guest lecturer, FMPH101, Epidemiology
    - Spring 2018, Winter 2018, Fall 2017
- Teaching Assistant and Guest lecturer, FPMU40, Intro to Public Health
    - Spring 2017
- Teaching Assistant and Guest lecturer, FPMU102, Biostatistics
    - Winter 2017, Spring 2016, Winter 2016

San Diego State University

- Guest lecturer and Teaching Assistant, PH302, Intro to Epidemiology
    - Fall 2014

San Diego Jewish Academy

- High school AP math and science teacher (2008-2012)

PUBLICATIONS

1. Marinac CR., **Nelson, SH**., Cadmus-Bertram, L., Kerr, J., Natarajan, L., Godbole, S., Hartman SJ. (Supportive Care in Cancer, September 2018) Dimensions of Sedentary Behavior and Objective Cognitive Functioning in Breast Cancer Survivors.
2. Wang WS, Ma JD, **Nelson SH**, Revta C, Buckholz GT, Mulroney C, Roeland EJ. (Supportive Care in Cancer, June 2018). Transfusion practices at end of life for hematopoietic stem cell transplant patients.
3. Xu, SY., Natarajan, L., **Nelson, SH**., Kerr, J., Godbole, S., Johnson, E., Patterson, R., Rock, C., Sears, D., Abramson, I. (Statistics in Biosciences, December 2017). Modeling temporal variation in physical activity using functional principal components analysis.
4. Hartman SJ, **Nelson SH**, Weiner LS. (Journal of Medical Internet Research, November 2017). Patterns of Fitbit Use and Activity Levels Throughout a Physical Activity Intervention
5. Hartman SJ, **Nelson SH**, Myers E, Natarajan L, Sears DD, Palmer BW, Weiner LS, Parker B, Patterson RE. (Cancer, August 2017). Randomized controlled trial of increasing physical activity on objectively measured and self-reported cognitive functioning among breast cancer survivors: The Memory & Motion study.

6. Wang WS, Ma JD, **Nelson SH**, Revta C, Buckholz GT, Mulroney CM, Roeland E. (J Onc Pract, June 2017) Advance Care Planning and Palliative Care Integration for Hematopoietic Stem Cell Transplant Patients.
7. **Nelson SH**, Brasky TM, Patterson RE, Laughlin GE, Kritz-Silverstein D, Edwards BJ, Lane D, Rohan TE, Ho GYF, Manson JE, LaCroix AZ. (Cancer Epidemiology, Biomarkers and Prevention, March 2017) The association of the C-reactive protein inflammatory biomarker with breast cancer incidence and mortality in the Women's Health Initiative.
8. Marinac CR, **Nelson SH**, Breen CI, Flatt SW, Natarajan L, Flatt SW, Pierce JP, Patterson RE. **(**Breast Cancer Research and Treatment, January 2017**).** Sleep Duration and Breast Cancer Prognosis: Perspectives from the Women's Healthy Eating and Living Study.
9. Hartman, SJ., **Nelson, SH**., Cadmus-Bertram, L., Patterson, RE., Parker, B., Pierce, JP**.** (American Journal of Preventive Medicine, November 2016). Technology- and Phone-Based Weight Loss Intervention: Pilot RCT in Women at Elevated Breast Cancer Risk.
10. **Roeland EJ,** Ma JD, **Nelson SH**, Seibert T, Heavey SF, Revta C, Gallivan A, Baracos V. (J Support Care Cancer. 2017 Feb) Weight loss versus muscle loss: re-evaluating inclusion criteria for future cancer cachexia interventional trials.
11. Monazzam, S., Goodell, PB., Salcedo, ES., **Nelson, SH.**, Wolinsky, PR. (Journal of Trauma and Acute Care Surgery, September 2016). When are CT angiograms indicated for patients with lower extremity fractures? A review of 275 extremities.
12. Xu, SY., **Nelson, SH**., Kerr, J., Godbole, S., Patterson, R., Merchant, G., Abramson, I., Staudenmayer, J., Natarajan, L. (Statistical Methods in Medical Research July 2016). Statistical approaches to account for missing values in accelerometer data: applications to modeling physical activity.
13. Tomlinson, M., Rotheram-Borus, MJ., LeRoux, I., Youssef, M., **Nelson, SH**., Scheffler, A., Weiss, R., O'Conner, M., Worthman, C. (Prevention Science, July 2016). Thirty-Six-Month Outcomes of a Generalist Paraprofessional Perinatal Home Visiting Intervention in South Africa on Maternal Health and Child Health and Development.
14. Rotheram-Borus, MJ., Tomlinson, M., Scheffler, A., Harris, D.M., **Nelson, S**. (AIDS and Behavior, June 2016) Adjustment of a Population of South African Children of Mothers Living With/ and Without HIV Through Three Years Post-Birth.
15. Cadmus-Bertram, L., **Nelson, SH**., Hartman, SJ., Patterson, RE., Parker, B., Pierce, JP**.** (Journal of Behavioral Medicine, March 2016). Randomized trial of a phone- and web-based weight loss program for women at elevated breast cancer risk: The HELP Study.
16. **Nelson, SH**., Marinac, CR., Patterson, RE., Nechuta, SJ., Flatt, SW., Caan, BJ., Kwan, ML., Poole, EM., Chen, WY., Shu, X., Pierce, JP. (Breast Cancer Research and Treatment, February 2016). Impact of very low physical activity, BMI, and comorbidities on mortality among breast cancer survivors.
17. Marinac CR, **Nelson SH**, Breen CI, Flatt SW, Hartman SJ, Natarajan L, Flatt SW, Sears DD, Pierce JP, Patterson RE. (JAMA Oncology, January 2016). Prolonged Nightly Fasting and Breast Cancer Prognosis.
18. Ma JD, Benn M, **Nelson SH**, Campillo A, Heavey SF, Cramer A, Revta C, Thornberry K, Roeland EJ**.** (Journal of Palliative Medicine. 2016 Mar) Exploring the Definition of an Informed Health Care Proxy.

Manuscripts in progress:

1. **Nelson, SH**., Weiner L., Natarajan L., Patterson RE., Hartman SJ. (In preparation) Patterns of objectively measured physical activity during chemotherapy for breast cancer.
2. **Nelson, SH**., Xu, SY., Godbole, S., Kerr J., Patterson RE., Natarajan L. (In preparation) Statistical corrections to account for missing wear when modeling associations with accelerometry measured physical activity.
3. **Nelson, SH**., Natarajan, L., Patterson RE., Hartman SJ., Godbole, S., Johnson E., Marinac CR., Kerr J. (American journal of health behavior, In submission) Physical activity change in a randomized trial: comparison of measurement methods.

SELECTED RESEARCH PRESENTATIONS

1. **Nelson, SH**., Marinac CR., Cadmus-Bertram L., Kerr J., Natarajan L., Godbole S., Hartman, SJ. (March 2017) Associations between sedentary and standing behaviors with cognitive function among breast cancer survivors. Poster Presentation at the Annual meeting of the Society of Behavioral Medicine. San Diego, CA.
2. **Nelson, SH**., Marinac CR., Patterson, RE., Pierce, JP. (December 2015) Post-diagnosis physical activity and comorbidities, not BMI, explain mortality risk in the after breast cancer pooling project. Poster Discussion at the San Antonio Breast Cancer Symposium. San Antonio, TX.
3. **Nelson, SH**., Marinac CR., Patterson, RE., Pierce, JP. (May 2015) Physical Activity and Comorbidities Attenuate the Risk of Obesity in the After Breast Cancer Pooling Project. Poster Presentation at the San Diego Epidemiology Research Exchange. San Diego, CA.
4. **Nelson, SH**., Todd, K. Kristan Jr., WB., French, K. (2006). The Effects of Exposing Embryonic Leech Motor Neurons to the “Wrong” Target. Poster presented at the Annual meeting of the Society for Neuroscience. Atlanta, GA

ADDITIONAL SKILLS

- Advanced knowledge of SAS programing
- Fluent in statistical computer packages (SPSS, PASS)
- Microsoft office suite (Excel, PowerPoint, Word)
- Excellent verbal and written communication skills

ABSTRACT OF THE DISSERTATION

Physical Activity Measurement in Breast Cancer Survivors:
Methodological Issues, Solutions, and Applications

by

Sandahl H. Nelson

Doctor of Philosophy in Public Health (Epidemiology)

University of California San Diego, 2018
San Diego State University, 2018

Professor Ruth Patterson, Co-Chair
Professor Loki Natarajan, Co-Chair

Background: Physical activity after a diagnosis of breast cancer is associated multiple positive effects. However, the literature indicates that patients' activity decreases during chemotherapy. Little is known about when during chemotherapy activity changes, as existing research has relied on self-reported data. Monitoring devices like accelerometers offer more objective measures, nevertheless, these devices may introduce other sources of measurement error.

Methods: Chapters 1 and 2 leverage data from Reach for Health (RFH), a trial that encouraged increased physical activity among breast cancer survivors. At baseline and study completion, participants wore accelerometers and answered the GPAQ. Chapter 1 uses the GPAQ estimates along with accelerometer measures, processed using standard cut-points and a machine learning algorithm, to assess agreement of activity estimates. Comparisons are assessed using mixed effects regression models. Chapter 2 uses a pseudo-simulation to generate missing wear patterns. The simulated and true data is used to compare 6 possible techniques to account for missing accelerometer wear. Chapter 3 analyzed the Activity in Treatment (ACT) study which enrolled 32 women prior to starting chemotherapy for breast cancer, all women were given a Fitbit activity monitor to wear throughout chemotherapy. Restricted cubic splines assessed non-linear patterns of activity.

Results: At baseline, self-report and machine learning provided similar activity estimates; while estimates of activity change were only similar between cut-point and machine learning, the magnitude of agreement with self-report was differential by group. Random slope imputation and an accelerometer specific multiple imputation performed best in correcting for missing wear time. MVPA declined linearly at an average of 1.4 min/day (p=0.002) for every 10% of the duration of chemotherapy that passed, while TPA declined linearly at an average of 13.4 min/day (p=0.0007) for every 10% of chemotherapy that passed. This decline occurred until approximately half way through chemotherapy. Additionally, a HER2+ receptor status was associated with a greater rate of decline in MVPA.

Discussion: Our findings highlight the importance of targeting physical activity interventions during active treatment for breast cancer and increases our ability to standardize research practices regarding the processing and analysis of physical activity data.

INTRODUCTION

Background

Approximately 1 in every 8 US women develops invasive breast cancer.[1] Fortunately, advances in breast cancer treatment have increased the 5-year survival rate to 91%.[2] This high incidence of breast cancer, combined with increased survival, has motivated research on lifestyle interventions that can empower patients to improve their quality of life and their cancer prognosis.

Data from animal and human studies suggest that physical activity after a diagnosis of breast cancer is associated with short- and long-term positive effects on treatment-related side effects, quality of life, and prognosis.[3-6] In addition, provocative new research in animals suggests that activity might also act to increase the efficacy of chemotherapy treatment.[7,8] Randomized controlled trials of physical activity during treatment for breast cancer indicate that exercise can be tolerated by cancer survivors[9] and helps lessen fatigue, improves physical fitness, and can improve quality of life.[10]

Understanding of Physical Activity Patterns in Cancer

Despite the positive effects of physical activity during active treatment, understanding of the natural trajectory of physical activity during treatment is limited. To date, outside of interventions, studies of physical activity during chemotherapy for breast cancer have been almost entirely limited to self-report assessment of activity levels (Table I.1).[11-19] There is one small (n=28) study, however, that used objective, accelerometer, measures.[17] It followed participants during only the first 14 days of chemotherapy and found that patients' accelerometer measured step count was less than 5000 steps/day, corresponding to an essentially sedentary lifestyle.[20] In addition, most studies queried physical activity only at several month intervals and so were unable to assess patterns of physical activity during treatment. Despite these limitations, almost all studies have found that physical activity decreased following diagnosis and treatment for breast cancer.[11,12,14,16,18,21]

In the several studies of free-living activity levels that incorporated accelerometers, all but one[17] focused on the physical activity following active treatment (Table I.2).[22-27] These studies indicate that breast cancer survivors have low physical activity levels that are considerably below recommended levels. However, these studies do not provide information regarding whether physical activity decreased at diagnosis, during chemotherapy, or after treatment. A better understanding of free-living patterns in physical activity *during* treatment for breast cancer would allow researchers to design more targeted interventions and help clinicians understand when their patients are most likely to need extra motivation to stay active, both of which could help to improve physical activity levels after treatment.

Self-Report and Objective Activity Measurement

As mentioned above, understanding physical activity behavior among cancer survivors has largely relied on self-reported data, which has considerable limitations, including social desirability and recall bias which may be affected by age, obesity, or cognition.[28] A 2016 study found that cancer patients enrolled in a lifestyle trial while undergoing chemotherapy self-reported moderate to vigorous physical activity (MVPA) levels 366% higher than was objectively measured.[29] Activity researchers are increasingly incorporating objective, accelerometer based, measures of physical activity. However, the increasing use of accelerometers coupled with the poor agreement with self-report makes the assimilation of past and future findings difficult. Increased use of accelerometers also limits study design, specifically when it is desirable to understand physical activity in the time before a participant would have been recruited, i.e. pre-diagnosis physical activity in a study only enrolling cancer patients. Self-report physical activity assessments are likely to be used in future studies because of the ease and low participant burden of self-report. At the same time there is a growing adoption of accelerometers for use in physical activity measurement. Thus, it is increasingly important to quantify agreement between the two forms of measurement and examine other methods of processing the accelerometer data that might bridge the divide between estimates from self-report and objective measures.

Agreement in Self-Report and Objective Activity Measurement

Agreement between self-report and objectively measured physical activity ranges (-.71 to 0.96), but is generally low to moderate.[30] Thus, choice of measurement method can have a huge and unpredictable impact on estimated levels of activity. This lack of agreement further calls into question the comparability of studies that use self-report versus those that use objective measures, as well as the accuracy of both measures given that they contain differing sources of bias. Self-report physical activity contains bias due to recall, social desirability, misclassification due to misunderstanding of terms, or use of a self-report measure that fails to capture the respondents' primary mode of physical activity.[28] Objective measures contain bias due to non-wear time and misclassification of activity by the measurement device. Specifically, when accelerometer data is processed using methods developed in young, active, participants, it might fail to recognize the lower absolute intensity seen in older participants' perceived vigorous activity, despite the activity being equal or greater in relative intensity.[31,32] This limitation is especially important in the cancer setting as breast cancer incidence is more than 7 times higher in women over fifty.[33] The difference between relative (activity intensity based on an individual's fitness level) and absolute intensity is another reason that self-report and accelerometer measurements in older adults or cancer patients with treatment related side-effects might have especially low agreement.

It has also been hypothesized that self-report and objective measurement capture different aspects of physical activity,[34] thus the measurement method used might affect the conclusions reached, for example regarding the benefits of physical activity on various risk biomarkers.[34] Celis-Morales et al. examined the relationship between self-report and accelerometer measured MVPA with biomarkers and found that self-report consistently overestimated MVPA, but that the relationship between biomarkers and MVPA were sometimes only significant with self-reported MVPA and sometimes only in accelerometry measured MVPA.[35] Understanding agreement between objective and self-report measures, and testing a method of accelerometer data processing that can better align these two measures, within a population of older adult breast cancer survivors, is vital. This understanding will help researchers make informed decisions regarding physical activity measurement in the design of future studies and will help with the interpretation and assimilation of findings regarding physical activity in breast cancer survivors.

Machine Learning

Machine learning is a method which uses objectively measured activity data plus the ground truth of the activity being performed to create an algorithm that can reliably predict the activity being performed in future activity recordings. In this way machine learning uses accelerometer measures to classify activity based on behavior rather than intensity, thus it may prove to be a way in which to process objectively measured physical activity that provides estimates that bridge the gap between self-report and standard objective measures. Machine learning has the ability to bridge the gap because someone with a lower fitness level will have a higher rating of perceived exertion for the same absolute level of physical activity intensity, for example, an accelerometer processed using standard intensity cutpoints would classify the activity as low, while a self-report account would classify it as moderate to vigorous. The machine learning processing classifies activity based on behavior patterns rather than intensity thus, when developed in a population with similar fitness levels, can help to capture estimates that more closely align with relative intensity, while removing biases associated with self-report.

Wear Time in Objective Activity Measurement

In addition to data processing, bias in accelerometer estimates may arise from variability in wear-time. Specifically; missing data due to participants removing their accelerometer for varying and undocumented reasons has the potential to introduce non-random error.[36] Previous studies have highlighted that error exists due to inconsistencies in the number of wear days[37] and the amount of wear time each day.[38,39] This variability in wear can lead to inaccurate assessments of physical activity[40] thus presenting an obstacle to accelerometer based research. To date, physical activity researchers have implemented a variety of techniques for dealing with missing data due to variability in wear time. These techniques include normalizing activity measures by wear time,[41-43] adjusting for wear time in regression models,[44,45] residualizing physical activity estimates, Bayesian correction techniques,[46,47] and various forms of imputation.[48-50] In addition, a recent multiple imputation technique has been developed specifically to apply to minute level accelerometer data.[51] Xu et al. also developed an inverse wear time weighting method for use in physical activity analysis when physical activity is the dependent variable of interest.[52] While these have been a useful advancement to the field, it is also very common in physical activity studies for the outcome of interest to be something other than physical activity (e.g., BMI or biomarkers). In this case any mismeasurement due to wear time is now in the *x* variable, thus validation of wear time corrections when the mismeasurement (due to wear time) was in the *y* variable cannot be assumed to apply.

Aim of the Dissertation

The overall aim of this dissertation is to investigate sources of error and bias in measures of physical activity among breast cancer survivors, test wear time correction methods, and make use of objective, continuous, activity measurement to characterize physical activity patterns during active treatment for breast cancer.

Chapter 1 and 2 of this dissertation leverage data from the Reach for Health (RFH) study. RFH is an NIH funded, randomized, controlled, weight loss trial that encouraged increased physical activity and reduced energy intake among 333 postmenopausal, overweight or obese breast cancer survivors. Women were randomly assigned to weight loss counseling versus educational materials over 6 months.[53] At baseline and at study completion all participants answered the Global Physical Activity Questionnaire (GPAQ), a well validated questionnaire that allows for the calculation of physical activity in metabolic equivalents (MET) units.[54,55] Participants also wore hip accelerometers at both baseline and study completion. Minute-level physical activity estimates from the accelerometer were processed into METs using standardized cutpoint processes[56] and using a supervised machine learning algorithm. This rich data source provides an ideal setting to examine error in physical activity estimates and test possible corrections among breast cancer survivors. Chapter 1 contributes to the literature by quantifying agreement between self-report and objective measures, examining how agreement may differ based on randomization group, and exploring the use of a supervised machine learning algorithm to help process objective physical activity measures in a way that provides physical activity estimates that are aligned with both self-report and standard objective measures. Chapter 2 provides a comparison and validation of correction techniques to account for variations in accelerometer wear time for use when physical activity is the independent variable of interest. This will add to the literature for which there is only validation when physical activity is the dependent variable of interest. Having wear time correction validated in multiple analytic situations will allow for standardization of techniques used in physical activity analysis.

The final component of this dissertation, Chapter 3, is the analysis of the Activity in Treatment (ACT) study. ACT is a pilot study that recruited 32 breast cancer patients who were scheduled to have chemotherapy at a UC San Diego Cancer Center. Prior to starting chemotherapy, participants were provided a wrist worn accelerometer (a Fitbit), and asked to wear it throughout the duration of their chemotherapy treatments. Enrolled patients were not asked to change their exercise habits. Fitbit data was collected through Fitabase, a database program that collects physical activity, heart rate and sleep data from the Fitbit cloud. In addition, cancer and infusion visit related variables were abstracted from participants' electronic medical records. Building on the evidence that physical activity is beneficial during active treatment, Chapter 3 aims to increase our understanding of patterns and changes in physical activity during treatment. The knowledge gained from Chapter 3 will help researchers build on randomized trials, which have highlighted the positive effects of exercise, to inform development of disseminable physical activity programs and better inform clinicians to enable their patients to stay physically active during this important time. This novel and important study provides in-depth objective data on the patterns of physical activity throughout chemotherapy. It also examines variables that may be associated with increased changes in physical activity during treatment. By gaining a better understanding of activity patterns and their relationship to chemotherapy, this study helps identify critical times at which to implement programs to increase physical activity among breast cancer patients, thus potentially increasing quality of life and prognosis.

In summary, this dissertation builds on the importance of physical activity in breast cancer survivors and the increasing focus on accelerometer measured physical activity by: quantifying error in the collection of physical activity data (Chapter 1), comparing approaches used to deal with these issues, specifically those related to wear time (Chapter 2), and bringing these findings to clinical relevance by measuring the trajectory of physical activity in patients undergoing chemotherapy treatment (Chapter 3).

Table I.1: Physical activity assessed *before and after* treatment for breast cancer

Title	Author (year)	n	country	Findings	Time frame	Timing of quesstionaire	PA Measurement
Reduced rates of metabolism and decreased physical activity in breast cancer patients receiving adjuvant chemotherapy	Demark-Wahnefried (1997)	18	USA	PA decreased significantly from baseline to study completion.	Recruited women scheduled to have chemo (post surgery/pre-chemo). Completed weekly questionnaires	before initiation and throughout chemotherapy	SR (Stanford Five-City Project Questionnaire)
Physical activity levels before and after a diagnosis of breast cancer The Health, Eating, Activity, and Lifestyle (HEAL Study)	Irwin (2003)	812	USA	decreased total PA by 2 hr/week pre to post diagnosis	year prior to diagnosis --> 4-12 months post diagnosis	Year prior to diagnosis and 4-12 months postdiagnosis (all assessed at same time)	SR (Modifiable Activity Questionnaire)
Physical activity levels among breast cancer survivors (HEAL)	Irwin (2004)	806	USA	32% of survivors participated in recommended levels of PA at 3 years post diagnosis	Year prior to diagnosis and 3 years post diagnosis	Year prior to diagnosis and 4-12 months postdiagnosis (all assessed at same time) + avg. 31 months post diagnosis	SR (Modifiable Activity Questionnaire)
Prospective, longitudinal study of leisure-time exercise in women with early-stage breast cancer	Andrykowski (2007)	231	USA	Prediagnosis to post treatment decrease in leisure time exercise. PA level rebounded to baseline levels at 6 months post treatment	before, during, and following treatment	pre-treatment, post radiation, post-chemo, 2 months post, 6 months post	SR (Leisure Time Exercise Questionnaire)
Longitudinal study of recreational physical activity in breast cancer survivors	Littman (2009)	315	USA	Recreational PA decreased 50% by 12 months post diagnosis (Rebounded some by 19-30 months post but not to original level)	2 years prior to diagnosis --> 12 and 30 month post diagnosis	baseline (2 years prior to baseline and since diagnosis) and at each follow-up visit	SR (Modifiable Activity Questionnaire) *Recreational PA only
Determinants of physical activity among women treated for breast cancer in a 5-year longitudinal follow-up investigation	Emery (2009)	227	USA	PA increased during first 18 months then declined steadily over next 42 months	post-diagnosis/pre-treatment --> every 4 months during first year	baseline (post diagnosis&surgery pre treatment) & every 4 months during 1st year, every 6 months next 4 years (12 total)	SR (7 day Physical Activity Recall)

Table I.1: Physical activity assessed *before and after* treatment for breast cancer (Continued)

Title	Author (year)	n	country	Findings	Time frame	Timing of quesstionaire	PA Measurement
Physical activity levels after treatment for breast cancer- ONE-year follow-up	Devoogdt (2010)	267	Belgium	PA significanlty decreased the first month post-op did not recover during first year.	Pre surgical PA --> 1,3,6,and 12 months post-surgery	1 day Pre surgical & 1,3,6,and 12 months post-surgery	SR (PA Computerized Questionnaire)
Physical activity levels after treatment for breast cancer- TWO-year follow-up	De Groef (2018)	267	Belgium	2 years post surgery all activity levels were still significantly lower then pre-surgery. No change from 1	Added a 24 month questionnaire to "one year follow up" paper	1 day Pre surgical & 24 months post-surgery	SR (PA Computerized Questionnaire)
Change on physical activity during active treatment in a prospective study of breast cancer survivors	Kwan (2012)	19,696	USA	Decrease in PA from diagnosis to around 8 months post-diagnosis	diagnosis to 8 months post-diagnosis	2 months post-diagnosis and 8 months post-diagnosis	SR (Arizona Activity Frequency Questionnaire)
Physical activity intensity and health status perception of breast cancer patients undergoing adjuvant chemotherapy	Tonosaki (2014)	28	Japan	First week of chemo 3841 steps/day, second week of chemo 4058 steps/day. Over 70% of day spent sitting.	First 14 days of chemotherapy	NA	Accelerometer

Table I.2: Physical activity assessed after treatment for breast cancer

Title		n	country	Findings	Time frame	Timing of PA measurement	PA Measurement
Objectively measured physical activity and sedentary time of breast cancer survivors, and associations with adiposity-findings from NHANES	Lynch (2009)	111	USA	BC survivors mostly light intensity (33%) and sedentary (66%)	Ten years post-diagnosis	7 day accelerometer. Avg 10 years from diagnosis	Accelerometers
Prospective Examination of Objectively Assessed Physical Activity and Sedentary Time after Breast Cancer Treatment - Sitting on the Crest of the Teachable Moment	Sebiston (2014)	177	Canada	78% of day sedentary, 2% of day in MVPA. Decreased MVPA by over 2 min/d in the 12 months post-treatment.	1 year following completion of treatment. (recorded 1 week every 3 months)	7 day accelerometer every 3 months for the year following treatment	Accelerometers
Testing the 'teachable moment' premise- does physical activity increase in the early survivorship phase	Broderick (2014)	24:20 case: control	Ireland	Less light activity then controls at 6 weeks post chemo completion (no change on PA between 6 weeks and 12 months post-chemo)	Recordings over first year after completion of chemo (compared to matched non-cancer controls)	7 day accelerometer at 6 weeks, 6 months, and 1 year post chemo completion (used matched controls as the "pre-chemo" level)	Accelerometer & SR (International Physical Activity Questionnaire)
Physical activity and fitness in women with metastatic breast cancer	Yee (2014)	71:71 case: control	Australia	Women with metestatic BC were less arobicly fit, had lower muscle strength, less daily PA then healty controls	Case control study avg 5 year post primary diagnosis	7 day accelerometer. Avg 2.9 years from onset of metestatic disease + healthy controls	Seanswear accelerometer & SR (Godin Leisure-Time Exercise Questionnaire)
Level of physical activity and characteristics associated with change following breast cancer diagnosis and treatment	Harrison (2009)	287	Australia	Small change 6-12 month post diagnosis. >50% were insufficiently active at each timepoint	6, 12, &18 months post diagnosis	6, 12, &18 months post diagnosis	SR (BRFSS)
Life after breast cancer-moving on sitting down or standing still-prospective study canadian breast cancer surviviors	Sebiston (2019)	201	Canada	TBD-Protocol paper	Regular intervals for 5 years post treatment	Every 3 months in the year post-treatment & 1 per year for next 4 years after	Accelerometers & SR (Leisure-Time Exercise Questionnaire & Short Questionnaire to Assess Health-enhancing PA)

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CHAPTER 1:

Physical Activity Change in a Randomized Trial:

Comparison of Measurement Methods

Sandahl H. Nelson, Loki Natarajan, Ruth E. Patterson, Sheri J. Hartman, Caroline Thompson, Suneeta S. Godbole, Eileen Johnson, Catherine R. Marinac, Jacqueline Kerr

ABSTRACT

Objectives: To quantify the agreement between self-report, standard cut-point accelerometer, and machine learning accelerometer estimates of physical activity, and examine how agreement changes over time among older adults in an intervention setting. **Methods:** Data were from a randomized weight loss trial that encouraged increased physical activity among 333 postmenopausal breast cancer survivors. Physical activity was estimated using accelerometry and a validated questionnaire at baseline and 6-months. Accelerometer data were processed using standard cut-points and a validated machine learning algorithm. Agreement of physical activity at each time point and change was assessed using mixed effects regression models and concordance correlation. **Results:** At baseline, self-report and machine learning provided similar physical activity estimates, but the cut-point and machine learning methods assessed physical activity change over time more similarly. **Conclusions:** Intervention researchers are facing the issue of self-report measures introducing bias and accelerometer cut-points being insensitive. Machine learning approaches may bridge this gap.

Introduction

Evidence regarding the public health importance of physical activity is incredibly robust, from decreasing incidence of heart disease[1] to warding off and helping to recover from some forms of cancer.[2,3] Studies are continuing to be designed to help hone physical activity guidelines, and trials are run to understand ways to increase physical activity, and to quantify the impact of increasing physical activity on various health markers and outcomes. It is important to public health that we continue to expand our understanding of physical activity measures while also developing strategies to increase physical activity. Thus, it is equally important to understand how the way in which we measure physical activity may affect our intervention findings and ultimately shape physical activity recommendations to the public.

The majority of physical activity research to date relies on self-report or accelerometry measures. Agreement between self-report and accelerometry measured physical activity is generally low to moderate, but with a wide range from -0.71 to 0.96.[4] Thus, choice of measurement method could have an impact on the reported levels of activity, as well as assessments of change in activity over time. This discrepancy is particularly important in randomized trials that need to determine participants' eligibility to enter a trial based on estimates of activity or seek to compare change in physical activity between conditions.

The lack of agreement between self-report and accelerometry methods does not predicate that one measurement should be used while the other is discarded, as both self-report and accelerometer measures are affected by different sources of systematic error. Self-report physical activity may be misclassified due to poor recall, social desirability (ie, over-reporting of activity), misunderstanding of terms, or use of survey items that fail to capture the respondents' primary mode of physical activity.[5] Recall bias may be of particular concern in older populations or cancer survivors whose treatment may have affected cognitive capacity.[6,7] Social desirability bias can be problematic in intervention trials, as one group may come into greater contact with study staff, leading them to potentially report greater activity improvements. At the same time, accelerometer measures are subject to measurement error due to differences in non-wear time (eg, if participants only wear devices on active days), number of accelerometer wear days deemed valid, missing activities such as swimming, or due to different decision rules used when processing the data. Specifically, standard intensity cut-point methods developed in young, active, participants may not perform well in all populations, such as older adults. As adults age, the threshold that constitutes vigorous activity changes and absolute cut-points may not take into account this physical limitation.[8,9] In older adults, the correlation between accelerometer counts and caloric expenditure is not linear, especially when assessed on a treadmill.[9] This difference between relative (activity intensity based on an individual's fitness level) and absolute intensity is one reason self-report and accelerometer measurements in older adults may have especially low correlations.[10] For example, given that many older adults prefer to walk, recall of this activity may be more accurate while accelerometer cut-points defined for a younger population may underestimate the same walking.

Machine learned algorithms have recently been developed for multiple population groups to potentially overcome the measurement error associated with employing single axis minute level absolute cut-points. Machine learning methods can employ data from the 3 axes of movement and extract feature vectors from the raw data signal.[11] Most algorithms, however, have been developed in the laboratory setting, which limits their application to real world cohorts. In contrast, Ellis et al. have developed algorithms using real world data, including in breast cancer survivors.[11] This specific machine learned algorithm was developed to classify activity based on behavior rather than intensity. Thus, we seek to assess whether, when developed in a free-living setting and in a population with similar fitness levels, machine learning behavior estimates may help to capture physical activity estimates that more closely align with relative intensity, while removing biases associated with self-report. While self-report and accelerometer measures have historically provided very different estimates, we hypothesize that they could be more closely aligned and that machine learning behavioral algorithms offer a way in which to process accelerometry data, focused on behavior rather than intensity, that could bridge the two and provide estimates that align with both self-report and standard accelerometer measures.

This study leverages data from *Reach for Health*, a weight loss trial that encouraged increased physical activity and reduced energy intake among 333 postmenopausal, overweight or obese breast cancer survivors.[12] The trial collected self-report and accelerometer measured physical activity at baseline and follow-up (6 months). Accelerometer measures were processed using standard cut-points and using a validated machine learning algorithm. The aim of this study was to quantify agreement between self-report, standard cut-point accelerometer, and machine learning accelerometer activity estimates and to examine how agreement may differ by randomization group over time. All with the goal of providing measurement method recommendations for future physical activity research to facilitate standardization of methods.

Methods

This study uses data from Reach for Health (RFH), a randomized, controlled, weight loss trial in non-diabetic breast cancer survivors, conducted at the University of California (UC) San Diego as part of the Transdisciplinary Research in Energetics and Cancer (TREC) Center initiative to examine the role of insulin resistance and inflammation in breast cancer risk.

Participants were recruited between August 2011 and May 2015 from San Diego and the surrounding communities. Informed consent was obtained from all participants, and the IRB granted ethics approval for the trial.

Details of the RFH Study are published.[12] In short, the RFH study was a 4-arm trial in 333 postmenopausal, overweight/obese (BMI $\geq$25 kg/m^2), women diagnosed with stage 1, 2, or 3 breast cancer within the past 10 years, with no eligibility restrictions placed on habitual physical activity levels. The trial used a 2x2 factorial design with all participants randomly assigned to weight loss counseling versus educational materials and to either Metformin or a placebo, resulting in a 4-arm trial, with all therapies conducted over 6 months. Metformin is a common oral diabetes medication that helps control blood sugar levels and is safe for non-diabetics. Because of the factorial design, Metformin was equally distributed between the counseling and educational material arms, and had no impact on physical activity measures, thus analysis only compared the weight loss versus control groups. Participants wore hip accelerometers (ActiGraph GTX3+) and completed the Global Physical Activity Questionnaire (GPAQ) at baseline and at 6-month follow-up.

Lifestyle Intervention Versus Control

The lifestyle intervention was delivered by trained lifestyle coaches via 12 motivational interview calls over the 6-month intervention. The 12 calls were scheduled with weekly frequency in the beginning of the intervention followed by monthly calls later in the intervention. Food-related weight loss strategies were discussed, and participants were given pedometers and encouraged to increase their physical activity levels to 300 min/week of moderate to vigorous physical activity (MVPA), primarily through walking. Women in the control group were given the 2010 US Dietary Guidelines for Americans and were contacted by study staff at 2 weeks, 1 month, and 3 months to encourage adherence to taking their pills (double blinded Metformin or placebo).

Data Collection

Self-reported physical activity: Prior to randomization and at study completion participants answered the Global Physical Activity Questionnaire (GPAQ), a validated questionnaire developed by WHO to estimate physical activity in a typical week.[13,14] The GPAQ collects information on physical activity accumulated in 3 domains; at work, in travel to and from places, and in recreational activities. The GPAQ estimates activity in a typical week by asking; time spent per day in vigorous (and as a separate question moderate) intensity activities in each of the 3 domains and asking, in a typical week, how many days one does vigorous (and as a separate question moderate) intensity activities as part of each of the 3 domains.[15] The answers to these questions are then processed to calculate the time of total physical activity on average per day as per the World Health Organization scoring guidelines.[16]

Accelerometer measures: All participants wore the ActiGraph (model GT3X+) at baseline (in the week prior to randomization) and at the 6-month follow-up (in the week prior to study completion). Participants were instructed to wear the ActiGraph on the right hip during all waking hours, excluding water-based activities (eg, swimming, showering) for 7 consecutive days. The ActiGraphs were initialized to collect data at 30 Hz. To apply the traditional cut-points, ActiGraph data was processed using the ActiLife software to create 60-s epochs with the low-frequency extension enabled. The data were then processed using the Choi algorithm in R[17] to define wear and non-wear minutes. Minute level physical activity estimates from the accelerometer were processed using the standard 1952 cut-point.[18] Time in moderate to vigorous physical activity (MVPA) was used to estimate physical activity time. As a sensitivity analysis we also examined accelerometer data processed using 1041 and 760 cut-points as these have been proposed to be more appropriate for older adults.[8]

Machine learning processed physical activity: The machine learning algorithm used in this analysis was specifically developed for this population of overweight/obese postmenopausal breast cancer survivors and its creation has been described in detail elsewhere.[11] In brief, for development of the machine learning algorithm 38 women wore an ActiGraph GT3X+ accelerometer on the right hip and a camera (a SenseCam) around their neck which captured images at 15 second intervals during waking hours over 7 free-living days. The activities captured by the pictures were manually annotated and served as the ground truth by which to develop the algorithm to process accelerometer measured activity. The machine learning algorithm used 39 statistical features with a random forest classifier and a hidden Markov model to predict 4 behaviors (sitting, standing, ambulation, and riding in a vehicle). The development and testing process was conducted in 38 women not eligible for (or included in) the current trial but who represented the population, The algorithm was further validated in another sample of 222 older women, independent from the testing phase.[19] In this analysis the machine learning estimate of ambulation time serve as the machine learning estimate of physical activity time.

Participant characteristics: Demographics data (age, ethnicity, and educational attainment) as well as Short Form Health Survey (SF-36) measures of mental and physical health were obtained via self-report at baseline. Weight and height were measured by trained study staff at baseline and were used to calculate BMI. Cancer related variables were obtained via medical chart abstraction. Details of measurement procedures are published.[12]

Statistical Analysis

Data preparation: Of the initial 333 women enrolled in the RFH trial, 289 (87%) had self-report and accelerometer measured physical activity at baseline and follow-up. For the purposes of this analysis only the 289 with complete physical activity data were included in the analytic sample.

For all physical activity analyses, the mean of the day level accelerometer and mean of the day level machine learning measurements were calculated (separately at baseline and follow-up) to provide single estimates of minutes per day. Collapsing daily measurements to a single estimate was done in order to match the units in self-report, which asks about average weekly activity and is scored to provide a single estimate of "minutes of total physical activity on average per day", as outlined in the World Health Organization analysis guidelines.[16]

Descriptive statistics: Descriptive statistics (mean/SD) were calculated for demographic variables at baseline, stratified by group (lifestyle intervention and control) and overall. We also calculated descriptive statistics (mean/SD) of the minute per day estimates of physical activity from each measurement technique: self-report (SR), accelerometer using machine learning processing (ML), and accelerometer using each of 3 cut-points: Freedson's 1952 cut-points (1952 CP), Copeland 1041 cut-points (1041 CP), and Matthews 760 cut-points (760 CP).[8,18,20] Descriptive statistics were calculated at baseline (pre-randomization), follow-up, and for the change between the time points (follow up – baseline), with follow-up and change statistics stratified by intervention group assignment. We also assessed estimates of the intervention effect on the change in activity, separately, using each physical activity measurement technique. This analysis was carried out using a mixed effects regression models of activity with a fixed effect terms for intervention group (lifestyle intervention or control), time-point (baseline or follow-up), and the time-by-intervention interaction. These models included a random intercept and used unstructured covariance as determined by AIC comparison. For all models, other than self-report, we also adjusted for the sum of accelerometer wear time at each time-point. The sum of wear time was used rather than daily wear time because daily accelerometer measurements were collapsed to a single estimate (as described previously in "data preparation"). Thus, the sum of wear time, rather than average, allowed us to control for the total amount of information gathered, ie, how many days the accelerometer was worn and for how long each day.

Comparison of agreement: Agreement of the estimates of min/day of physical activity at baseline, at follow-up, and the change (follow up – baseline) were examined pairwise between self-report, accelerometer using machine learned processing, and accelerometer using only 1952 cut-points. Statistical analysis of the agreement between measures was carried out by calculating descriptive statistics (mean, SD), Bland-Altman limits of agreement, and the concordance correlation for each pairs' difference at baseline, follow-up, and for the activity change (follow up – baseline).[21] We also calculated the Pearson and Spearman correlation for each of these comparisons. All analyses were stratified by lifestyle intervention with the exception of baseline data which was assessed with the groups combined, as this measurement was prior to randomization (results presented in Table 1.2).

To test for statistical significance of the difference between measurement techniques, in a way that accounts for the correlated nature of the measurements nested within individuals, we used a linear mixed effects model with a random intercept. This modeled physical activity as the outcome and included a fixed effect terms for measurement method, time (baseline versus follow-up), group (control versus intervention), as well as all 2- and 3-way interactions between these variables. Appropriate model contrasts were used to test if there were measurement method differences in estimates of (i) activity at baseline and follow-up, (ii) change in activity in each arm (2-way interactions) (iii) group differences in change in activity (3-way interactions), results presented in Table 1.3.

Results

Participants

At baseline, women in the study were on average 62.8 years old (SD=7.03), predominantly white (83.4%), non-Hispanic (88.2%), with a college education or greater (50.9%). Participants were an average of 2.6 years post-surgery (SD=1.93); 48.8% had Stage 1 breast cancer, 51.9% had received chemotherapy, and 70.2% had received hormone therapy. The average BMI was 31.1 kg/cm^3 (SD=4.97), participants had an average self-reported physical health score of 46.2 (SD=8.81) and mental health score of 51.3 (SD=9.18). **Table 1.1** presents these demographics, stratified by intervention group. There were no significant baseline differences between study arms, all p > .05.

Table 1.1: Characteristics of Overweight/Obese Breast Cancer Survivors in a Randomized Controlled Trial, Stratified by Intervention Group (N = 298)

Variable	**Control (N = 146)**	**Lifestyle Intervention (N = 143)**
	mean (SD)	*mean (SD)*
Age	62.6 (6.94)	63.0 (7.13)
Age at diagnosis	60.0 (6.76)	60.3 (7.30)
Years from Diagnosis to study	2.5 (1.78)	2.7 (2.09)
Physical Health (SF-36†)	46.0 (9.06)	46.3 (8.57)
Mental Health (SF-36†)	50.5 (9.54)	52.1 (8.76)
BMI	31.1 (5.01)	31.1 (4.94)
	n (%)	*n (%)*
White	123 (84.2%)	118 (82.5%)
Non-Hispanic	132 (90.4%)	123 (86.0%)
College education or greater	74 (50.7%)	73 (51.0%)
Received Chemotherapy	77 (52.7%)	73 (51.0%)
Received Hormone Therapy	107 (73.3%)	96 (67.1%)
Breast cancer stage		
I	67 (45.9%)	74 (51.7%)
II	50 (34.2%)	49 (34.3%)
III	29 (19.9%)	20 (14.0%)

†: Score based on the SF-36 self-report questionnaire, ranges 0-100 with higher scores corresponding to better health

Activity Distribution and Intervention Main Effects by Measurement Technique

Average minutes per day of physical activity at baseline, follow-up, and the change (follow up – baseline) are presented in **Table 1.2** for each of the measurement techniques (self-report, machine learning, Freedson 1952 accelerometer cut-point, Copeland 1041 accelerometer cut-point, and Matthews 760 accelerometer cut-point). As the baseline measurement period was pre-randomization and there were no significant differences between control and intervention group ($p > 0.1$) the groups remained combined at baseline. Self-report physical activity at baseline was 56.2 (SD=76.48) min/day; the controls showed an increase in 22.7 min/day versus an increase of 36.9 min/day in the intervention group. Machine learning estimates at baseline were similar to self-report, with an average min/day of 67.8 (SD=41.08). Unlike with self-report, machine learning estimates for controls show a decrease of 4.9 (SD=29.50) min/day, while the intervention group shows an increase of 7.7 (SD=35.88) min/day. Freedson, 1952, cut-point estimates provide the lowest baseline measures with an average of 20.0 (SD=18.51) min/day. The controls show a decrease of 2.0 (SD=13.34) min/day, while the intervention group shows an increase of 2.4 (SD=17.16) min/day. The Copeland, 1041, cut-point baseline estimate was 62.0 (SD=35.46) min/day, controls show a decrease of 4.3 (SD=22.75) min/day, while the intervention group shows an increase of 1.6 (SD=28.95) min/day. Matthews, 760, cut-point estimates provide the highest baseline measures with an average of 95.3 (SD=45.81) min/day. The controls show a decrease of 5.5 (SD=28.92) min/day, while the intervention group shows an increase of 0.2 (SD=36.11) min/day. Assessment of the statistical significance of the intervention effect on physical activity change (ie, the difference in activity change between groups) was non-significant when measured by self-report ($p = 0.18$). With both the machine learning and accelerometry using the standard 1952 cut-point we found a significant intervention effect for the change (difference of change) in physical activity (p = .003 and .028 respectively). Similar to self-report, the Copeland (1041) and Matthews (760) accelerometer cut-point did not detect a significant intervention effect (p = .095 and .235 respectively).

Table 1.2: Distribution of Activity, Among Overweight/Obese Breast Cancer Survivors in a Randomized Controlled Trial, as Measured by Self-Report, Accelerometry with Machine Learning, and Accelerometry with Standard Cut-Point. Stratified by Time and Intervention Group (N = 298; $N_{control}$ = 146, $N_{lifestyle\ intervention}$ = 143).

	Baseline	**Follow-up (6 month)**		**Change (Follow-up - Baseline)**		**Group difference of change**	
MVPA min/day by measurement (SD)	**Pre-randomization**	**Control**	**Lifestyle Intervention**	**Control**	**Lifestyle Intervention**	**β**	**p-value**
Self-report	56.2 (76.48)	72.6 (83.34)	99.7 (121.12)	22.7 (77.12)	36.9 (101.15)	14.21	.18
Machine Learning†	67.8 (41.08)	61.5 (35.95)	76.7 (46.33)	-4.9 (29.50)	7.5 (35.88)	11.5	.003*
Accelerometer							
1952 CP	20.0 (18.51)	17.1 (14.81)	23.3 (22.74)	-2.0 (13.34)	2.4 (17.16)	3.96	.028*
1041 CP	62.0 (35.46)	55.0 (31.54)	66.3 (36.47)	-4.3 (22.75)	1.6 (28.95)	5.09	.095
760 CP	95.3 (45.81)	85.8 (41.59)	99.6 (45.47)	-5.5 (28.92)	0.2 (36.11)	4.54	.235

*: Significant difference of change between groups (P < .05)
†: Ambulation min/day used as estimate of MVPA min/day

Due to non-significance of the intervention effect over time with the lower accelerometer cut-points, we carried out the remaining comparisons using only the 1952 cut-point. Physical activity over time, stratified by group, for each of the 3 measurement techniques - self-report, accelerometer cut-point (1952), and machine learning - are depicted graphically in **Figure 1.1**. This figure shows that baseline estimates are similar when measured using self-report or machine learning but are lower using 1952 cut-points, regardless of intervention group. It also illustrates that the trajectory of change is similar when measured by machine learning or 1952 cut-points, but that the trajectory of change is larger (in both the control and intervention group) when measured by self-report.

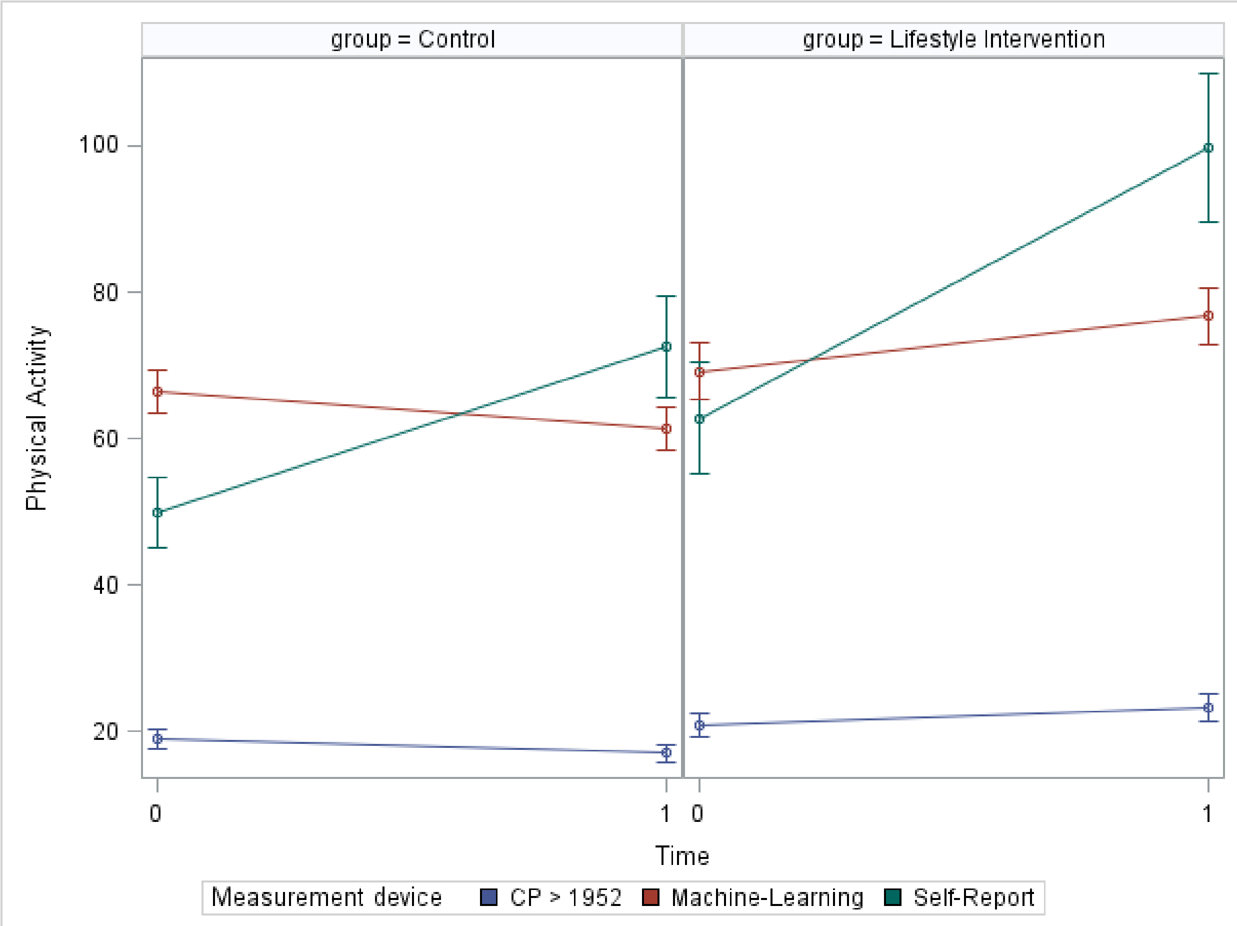

Figure 1.1: Physical Activity Change Over Time, Among Overweight/Obese Breast Cancer Survivors in a Randomized Controlled Trial, Stratified by Group, for Each of the 3 Physical Activity Measurement Techniques (N = 298).

Agreement Between Self-Report, Machine Learning, and Standard Accelerometry

A formal pairwise comparison of self-report, machine learning, and accelerometry using the 1952 cut-point (chosen given its sensitivity to detect change) is presented in **Table 1.3** stratified by intervention group for post-randomization assessment. Baseline values show statistically significant concordance correlation (r_c) between each pairwise comparison, as well as significant Pearson (r_p) and Spearman (r_s) correlation (**Table 1.4,** supplementary table). Despite statistical significance, baseline correlation was low ($r < .5$) for all comparisons, with the exception of Pearson and Spearman correlation between machine learning and 1952 cut-points ($r_p = .62$ and $r_s = .58$). At baseline, our mixed effects regression analysis showed a significant difference between the 1952 cut-point estimate and both the self-report and machine-learning activity estimates, with difference estimate of 36 and 48 minutes per day respectively ($p < .001$). Baseline estimates of self-report and machine learning were also significantly different ($p = .002$), but with a smaller magnitude of difference (11.5 min/day).

Table 1.3: Comparison of Self-Report, Machine Learning, and 1952 Cut-Point Physical Activity Measures Among Overweight/Obese Breast Cancer Survivors in a Randomized Controlled Trial (N = 289).

Time	Comparison	Mean difference min/day(SD)	Concordance Correlation	CC Lower	CC upper	Mixed effects p-value
Baseline	**Overall (N = 289)**					
	SR -ML	-11.5 (75.10)	0.26	0.14	0.38	.002
	SR - Accel	36.3 (72.09)	0.13	0.07	0.18	< .001
	ML - Accel	47.8 (33.43)	0.23	0.17	0.29	< .001
Follow-up (6 months)	**Lifestyle Intervention (N = 143)**					
	SR -ML	23.0 (114.19)	0.22	0.12	0.31	< .001
	SR - Accel	76.5 (115.33)	0.09	0.05	0.13	< .001
	ML - Accel	53.4 (34.65)	0.27	0.2	0.33	< .001
	Control (N = 146)					
	SR -ML	11.1 (87.84)	0.06†	-0.06	0.18	.061
	SR - Accel	55.5 (82.20)	0.04†	0	0.08	< .001
	ML - Accel	44.4 (27.65)	0.21	0.16	0.27	< .001
Change (Follow-up - Baseline)	**Lifestyle Intervention (N = 143)**					
	SR -ML	29.4 (103.50)	0.07†	-0.03	0.16	.001
	SR - Accel	34.6 (100.72)	0.03†	-0.02	0.08	< .001
	ML - Accel	5.1 (30.55)	0.4	0.3	0.5	.545
	Control (N = 146)					
	SR -ML	27.6 (81.32)	0.03†	-0.07	0.13	.001
	SR - Accel	24.7 (77.75)	0.01†	-0.04	0.06	.003
	ML - Accel	-2.9 (26.76)	0.31	0.21	0.42	.727

†= Non-significant correlation coefficient

(SR) = Self-Report, (ML)= Machine learning, (Accel) = 1952 Cut-point accelerometry, (CC) = Concordance correlation

Comparison of follow-up PA estimates, stratified by group, found a significant concordance correlation between each pairwise comparison among the intervention group, although the correlation values were again low ($r_c < .35$). Within the control group only the comparison of machine learning and 1952 cut-points showed significant concordance correlation. All comparisons still showed significant Spearman correlation, although Spearman correlation estimates were lower in the control group. This is notable as Spearman correlation indicates similar ranking of participants, an attribute that is important to maintain if association between physical activity and another trait (eg, biomarkers) is of interest. The comparison of follow-up physical activity estimates from our mixed effects regression analysis showed significant differences in estimates for all comparisons, with the exception of the comparison between machine learning and self-report within the control group only ($p = .061$).

Concordance correlation of the change estimates between self-report and both machine learning and standard accelerometry were low (essentially zero, $r_c < .07$) and non-significant, regardless of group – this was also the case for Pearson correlation ($r_p < .12$). The correlation of ranking, as measured by Spearman correlation, showed significant correlation of the change estimate between all measurement techniques in the intervention group, however in the control group only machine learning and the 1952 cut-points showed significant agreement of ranking (Spearman correlation). This indicates that there is a differential level of agreement between measurement techniques in the control and intervention group for the ranking of each participants' physical activity change.

Discussion

In this study we undertook an in-depth comparison of self-report, cut-point accelerometry, and machine-learning accelerometry methods for measuring physical activity and physical activity change within the context of a randomized lifestyle intervention trial.

Baseline Physical Activity Comparisons

In our comparison of baseline, pre-randomization, measurements we found that standard 1952 cut-point accelerometry had much lower estimates of physical activity then self-report, which aligns with previously published findings comparing the International PAQ (IPAQ) with 1952 cut-point accelerometry.[22,23] We also replicated results which found that that machine learning activity estimates were much higher than the 1952 cut-point estimates.[24] A novel finding was that machine learning activity estimates closely matched self-report and 1041 accelerometry cut points, while 760 cut-point provided much higher estimates. These findings in lower cut-points were contrary to a 2015 analyses within the Women's Health Study,[25] which found both the 1041 and 760 cut-points provided lower estimates for the percent of women meeting 150 min/wk of MVPA than their self-report survey. This discrepancy may be explained by the use of a Women's Health Study specific questionnaire for self-report physical activity, as opposed to the GPAQ used in our study, and raises the importance of standardizing self-report questionnaires. A second study which compared physical activity using self-report (Active Australia Survey) and accelerometry (1952 cut-point) in a randomized controlled trial of physical activity among male and female type 2 diabetics[26] also found that, at baseline, self-report measures were lower than accelerometry measures, a difference again possibly explained by the difference in the self-report measure used; it could also be due to the use of physical activity (based on self-report) as a known eligibility criteria for entry into the study, which was not a criteria for entry into the study we assessed, thus causing participants to underreport physical activity in a conscious or unconscious effort to gain entry into the study.

The findings from our baseline comparison has implications for cross-sectional studies and for eligibility screening in future randomized trials. In particular, if physical activity guidelines are developed mostly from self-reported evidence[27] then the 1952 cut-point would greatly underestimate the number of people meeting guidelines, especially older adults. Thus, for eligibility screening or cross-sectional analysis interested in how well people are meeting guidelines, the GPAQ self-report, machine learning, or 1041 accelerometry cut-point appear to provide similar estimates and would more closely align with current PA guidelines.

Physical Activity Change Comparisons

In our examination of change in physical activity we found notable differences between measurement techniques. Self-report estimates showed large increases in physical activity among both the intervention and control group, while accelerometry methods (machine learning and cut-points) detected only modest increases in the intervention group and showed decreases among the control group. Our findings are consistent with the examination of change in a previous study assessing agreement in physical activity change between self-report (IPAQ) and accelerometry (1952 cut point) in a single arm trial of physical activity in Latina women[23] which found that participants self-reported far greater increases in moderate physical activity then were detected by the accelerometer (median 232 min/week increase versus a 65 min/week increase respectively). Another study, previously referenced, that compared physical activity change using self-report (Active Australia Survey) and accelerometry (1952 cut-point) in a randomized controlled trial of physical activity[26] also found that the measurement difference (between self-report and 1952 cut points) increased following the intervention, but unlike in our study, they found that the magnitude of the difference was greater in the intervention group then in the control group. We also observed a weakening of the correlation between self-report and accelerometry (machine learning and 1952 cut point) at follow-up as compared to the baseline. A finding that, in the self-report and 1952 cut point comparison, has been previously seen.[28,29] A novel finding in our study was the greater decline in correlation between self-report and accelerometry (machine learning and 1952 cut points) seen among the control group as compared to the intervention group. A finding which was not seen between the machine learning and 1952 cut point measures. Change estimates measured by machine learning and 1952 cut points were significantly correlated (regardless of intervention group) but were both uncorrelated and meaningfully different (on the order of about 30 min/day) from self-report. The difference in correlation following the intervention, and concomitant difference in change estimates, between self-report and accelerometry that was seen in these studies, and in our own, may stem from an increase in social desirability bias after completion of a study that included contact with study staff. Or may stem from a genuine over-estimation of the activity in an 'average day' especially after randomizing participants to an intervention which increased focus on daily physical activity. Regardless of the underlying reason, these finding supports the use of accelerometry, rather than self-report, in studies where change in physical activity is an outcome of interest, especially when change is compared between groups.

This study also assessed differences, based on measurement technique, in study findings regarding physical activity in the context of a randomized intervention trial. In randomized trials it is the difference in physical activity change between groups that is often the most important statistical parameter. Here we find that only the machine learning and 1952 cut-points provide sensitive enough measurements to detect a significant difference in physical activity change, thus, supporting the use of one of these measurements in randomized trials.

Limitations

It is important to note that this study was conducted in a specific population; overweight, post-menopausal, breast cancer survivors and thus may not be generalizable to another population. While this is a potential limitation it is also a strength as it is generally less active populations for which we target our physical activity studies and interventions. In addition, understanding measurement differences for physical activity among older adults is of particular importance in breast cancer patients and survivors, as breast cancer incidence is more than 7 times higher in women over fifty[30] and the benefits of physical activity in breast cancer patients and survivors[31-34] makes physical activity research in this population an important and expanding field of study.

The examination of different cut points is also limited by the inclusion of only women, as physical activity in men may be detected differently by cut-point accelerometry. Another important consideration is the fact that the machine learning algorithm used in this study was designed specifically for this population, thus use of a less specific algorithm may not perform as well and designing an algorithm in the case of each study may not be feasible. Lastly is the fact that machine learning categorizes physical activity by presence of ambulation while cut points categorize physical activity by magnitude of the activity, thus “Moderate to Vigorous Physical Activity” (MVPA) would no longer be an applicable term. At the same time, it is potentially much more feasible for the general public to interpret prescribed activity (ie, “walk 30 min/day”) then to interpret prescribed intensity (ie, “spend 30 min/day being moderate to vigorously active”).

Given these limitations, future studies should include participants of various age and activity ranges, as well as men, to further validate our findings, especially those regarding the use of machine learning accelerometry. In addition, studies should be carried out which use less precisely tailored machine learning algorithms to assess how closely the training population must match the study population before the gains in sensitivity seen in machine learning over cut-point accelerometry are lost.

Interpretation of Findings

The goal of this study was to present findings to inform measurement methods for future physical activity studies and in interpreting the findings of existing studies. In populations such as the one examined here, if the parameter of interest is accurate cross-sectional physical activity estimates then self-report, accelerometry with 1041 cut-points, and machine learning appear to provide similar estimates. If the parameter of interest is change in physical activity, then self-report should be avoided, and an accelerometry based method should be used. Lastly if the goal is detecting a difference of change between groups then machine learning and 1952 cut-points both appear to have appropriate sensitivity. Thus, if a study seeks to use one measurement method to examine all 3 of these things; baseline physical activity levels, estimates of change, and detection of a difference in physical activity change between groups, then our findings recommend machine learning as an objective and therefore minimally biased measurement option, that still provides adequate sensitivity to detect change between groups.

Conclusion

Intervention researchers are facing the issue of self-report measures introducing bias and accelerometer cut-points being insensitive. Machine learning algorithms can provide a new approach to bridge this gap. While we may still wish to analyze multiple approaches to be able to compare to previous literature, the study's question of interest should be accounted for when deciding on the primary assessment protocol.

**Chapter 1 is currently in submission for the publication of the material. Co-authors include Dr. Loki Natarajan, Dr. Ruth Patterson, Dr. Sheri Hartman, Dr. Caroline Thompson, Suneeta Godbole, Eileen Johnson, Dr. Catherine Marinac, and Dr. Jacqueline Kerr. The dissertation author was the primary investigator and author of this material.*

Table 1.4: Pearson and Spearman correlation analysis of self-report, machine learning, and 1952 cut-point physical activity measures (n=289)

Time	Comparison	Pearson r	Pearson r p-value	Spearman r	Spearman p-value
Baseline	**Overall (n=289)**				
	SR -ML	0.33	<.0001	0.36	<.0001
	SR - Accel	0.36	<.0001	0.42	<.0001
	ML - Accel	0.62	<.0001	0.58	<.0001
Follow-up	**Lifestyle Intervention (n=143)**				
	SR -ML	0.34	<.0001	0.38	<.0001
	SR - Accel	0.00	<.0001	0.45	<.0001
	ML - Accel	0.69	<.0001	0.68	<.0001
	Control (n=146)				
	SR -ML	0.09	0.295 †	0.18	0.030
	SR - Accel	0.17	0.046	0.26	0.001
	ML - Accel	0.70	<.0001	0.68	<.0001
Change ***(Follow-up - Baseline)***	**Lifestyle Intervention (n=143)**				
	SR -ML	0.11	0.187 †	0.21	0.010
	SR - Accel	0.11	0.193 †	0.23	0.006
	ML - Accel	0.53	<.0001	0.54	<.0001
	Control (n=146)				
	SR -ML	0.05	0.590 †	0.16	0.056 †
	SR - Accel	0.04	0.638 †	0.14	0.099 †
	ML - Accel	0.42	<.0001	0.46	<.0001

(SR) = Self-Report, (ML)= Machine learning, (Accel) = 1952 Cut-point accelerometry, (r)=Correlation coefficient, † = Non-significant correlation coefficient

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CHAPTER 2:

Accelerometer Measured Physical Activity:

Methods to Account for Missing Wear

Sandahl H Nelson, Selene Yue Xu, Suneeta Godbole, Ruth Patterson, Caroline Thompson, Jacqueline Kerr, Sheri Hartman, Loki Natarajan

Abstract

Purpose: To compare correction techniques that account for error due to missing accelerometer wear time, for use when examining the independent effect of physical activity on health-related dependent variables.

Methods: We used a pseudo-simulation approach to generate missing wear, based on observed missing data patterns, in complete wear days (> 12 hr wear) among 328 female participants of the Reach for Health (RFH) study. Six possible techniques to account for missing accelerometer wear were separately applied to the simulated data. Results from regression models of BMI on moderate to vigorous physical activity (MVPA) or total activity were compared to the true data.

Results: Adjusting for wear time in regression models and residualizing physical activity resulted in lower coverage than applying no correction. Random slope imputation and an accelerometer specific multiple imputation performed best with regard to power.

Conclusion: Use of a random slope imputation or accelerometer specific multiple imputation could help negate the error due to missing accelerometer wear time. These methods are easy to use and could reduce disposal of days with low wear while helping to standardize accelerometer analysis.

Introduction

Personal monitoring devices, such as hip-worn accelerometers, offer more objective measures of physical activity than survey methods, and are becoming the recommended norm in physical activity research as they are seen to be less prone to the biases associated with self-report.[1,2] Nonetheless these devices may introduce other sources of measurement error and bias.[3-5] For example, missing data due to participants removing their accelerometer for varying and undocumented reasons leads to non-random bias. This in turn makes it difficult to accurately assess physical activity[6] and presents an, often overlooked, obstacle to the analysis and interpretation of accelerometer measured physical activity.

Previous studies have highlighted that both random and systematic error exists in accelerometer physical activity estimates due to inconsistencies in the number of wear days across participants[3] and the amount of wear time each day.[4,5] To date, physical activity researchers have implemented a variety of techniques in an attempt to account for this missing data and adjust for the variability in wear time. These techniques include normalizing activity measures by wear time,[7-9] adjusting for wear time in regression models,[10,11] residualizing physical activity estimates, Bayesian correction techniques,[12,13] and various forms of multiple imputation.[14-17] All in an attempt to produce physical activity estimates as close to the objective truth as possible, despite subjective variability in participant wear time.

Xu et al. examined wear time correction methods for use in physical activity analysis when physical activity was the dependent (i.e., outcome) variable of interest.[18] However, it is also very common for physical activity to be the independent variable (*x*) with the dependent outcome of interest (*y*) health related (e.g. BMI or biomarkers). In which case, any mismeasurement due to wear time affects the independent variable (*x*). Additionally, when physical activity is the independent variable, the dependent outcome of interest is usually not also measured at the day level, so day level physical activity estimates must be condensed into average estimates. Thus, validation of wear time correction methods for physical activity as the dependent outcome variable (*y*) may not be relevant for the independent variable (*x*) scenario.

In this study we used a pseudo-simulation approach to simulate missing data patterns in the Reach for Health (RFH) study,[19] a randomized controlled weight loss trial in female breast cancer survivors. Specifically, we considered days with > 12 hours of wear to be "complete" profiles. Within this complete dataset, we simulated missing wear patterns based on observed missing data patterns in the full RFH cohort. The RFH trial implemented a minimum wear criterion for entry into the study and requested re-wears for participants with low wear time, thus it attained a high level of device wear time compliance and offers an excellent opportunity to examine the effect of missing wear data and possible corrections to account for it. Various wear time corrections were applied to the simulated "missing" data and results were then compared to the true complete data. The wear time corrections tested were ones regularly used in physical activity research as well as emerging techniques shown to be good candidates based on previous work with physical activity as the dependent variable.[7-11,17,18]

The goal of this study is to compare correction techniques for use when physical activity is the independent variable and day-level physical activity must be condensed into week-level estimates. In doing so we hope to ascertain the optimal wear time correction technique for use when examining the independent effect of physical activity on health-related dependent variables. Identifying an optimal correction will serve to reduce the need to omit days with insufficient wear, consequently increasing power and lowering participant burden, and will allow for the standardization of techniques used in physical activity analyses.

Methods

Study Sample

This study uses baseline, pre-randomization, data from Reach for Health (RFH), a weight loss trial in non-diabetic, postmenopausal, breast cancer survivors, conducted at the University of California (UC) San Diego as part of the Transdisciplinary Research in Energetics and Cancer (TREC) initiative to examine the role of insulin resistance and inflammation in breast cancer risk. Participants were recruited between August 2011 and May 2015 from San Diego and the surrounding communities. Informed consent was obtained from all participants, and UC San Diego IRB granted ethics approval for the trial.

Details of the RFH trial are published elsewhere.[19] Briefly, the RFH study was conducted with 333 postmenopausal, overweight/obese (BMI $\geq$25 kg/m^2), women diagnosed with stage 1, 2, or 3 breast cancer within the past 10 years, with no eligibility restrictions placed on habitual physical activity levels.

Study Measures

Physical activity (PA) data was collected using a hip worn accelerometer. Prior to randomization each participant was instructed to wear an ActiGraph (model GT3X+) accelerometer (ActiGraph, Pensecola, FL) on the right hip for 7 days during all waking hours, excluding water-based activities (e.g. swimming, showering). Data were downloaded after the wear period and screened for completeness and irregularities. Participants were asked to re-wear the accelerometer if it was not worn for at least 10 hours per day for 5 days, or on 4 days with a total of 3000 minutes of wear.

Demographic data (age, ethnicity, and educational attainment) as well as Short Form Health Survey (SF-36) measures of mental and physical health were obtained via self-report at baseline. Weight and height were measured by trained study staff at baseline and were used to calculate BMI. Cancer related variables were obtained via medical chart abstraction.

Analytic Approach Overview

Figure 2.1 outlines the analytic approach of this study. Of the initial 333 women enrolled in the RFH trial, 328 (98%) women had at least one day of complete Actigraph wear (defined as ≥ 12 hr/day of wear[4,5]) for a total of 2091 complete wear days that made up the *true data* set. Non-wear time was classified using Choi's criteria[20] and standard calibration thresholds were used to aggregate data into minutes spent in light, moderate, and vigorous activity using the Freedson cut points.[21] A pseudo simulated data set was then created using these complete wear days. The pseudo simulation method has been described previously.[18] In short, patterns of missing wear from the full cohort were used to generate a simulation algorithm that created a realistic missing data pattern. This pseudo simulation was carried out multiple times (n=100) to create data sets with "realistic" missing wear time (*simulated data*). All simulated days, with no minimum threshold for total wear time remaining in the day, were retained. This simulated data, along with the complete *true data,* makes up the final data set used to examine the correction potential of 6 strategies to account for missing wear in the modeling of health outcomes putatively associated with physical activity. In the analysis we tested the effect of physical activity on BMI, where physical activity was the mean minutes of total physical activity (light, moderate, and vigorous activity), or mean minutes of MVPA (moderate and vigorous physical activity), averaged across the participants' wear days.

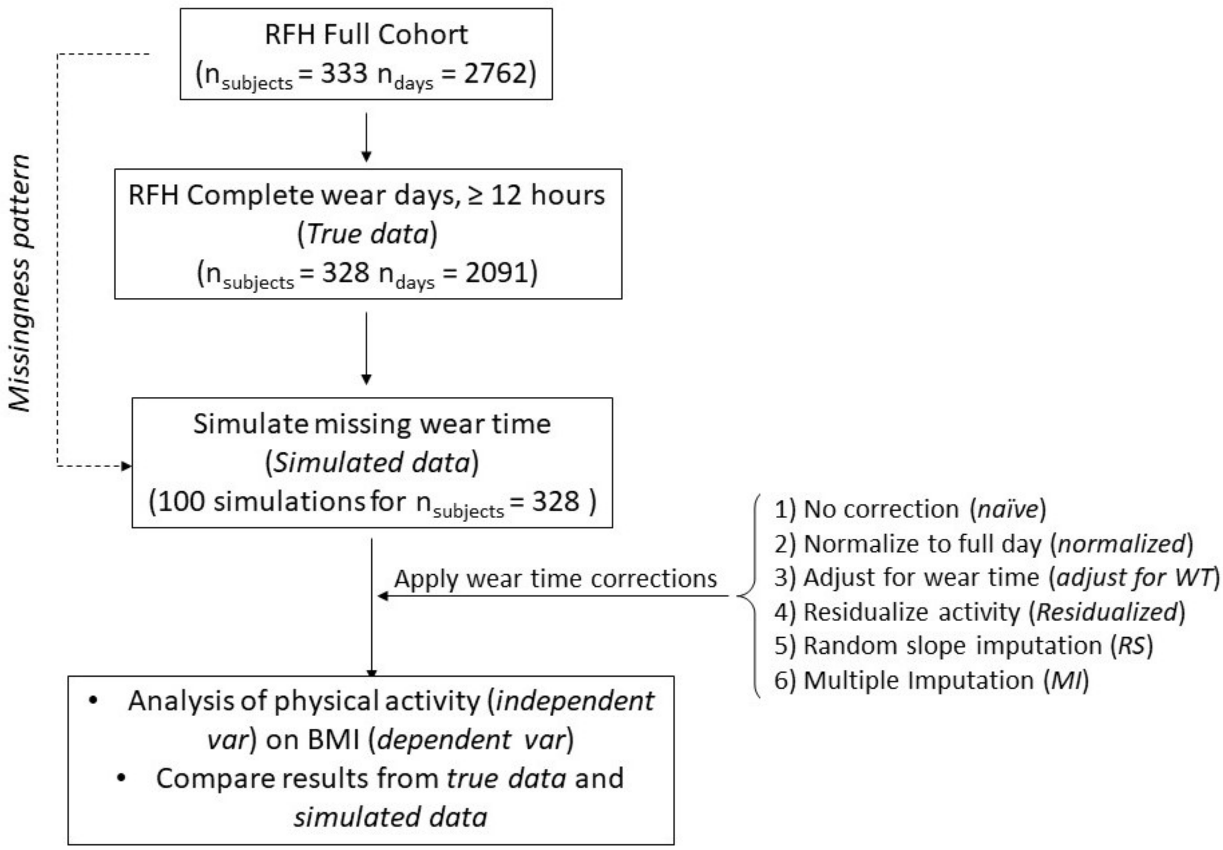

Figure 2.1: Study Schematic

Missing Data Correction Methods

The correction methods are as follows:

1. No correction (*Naïve)*: For this method no correction is implemented on the simulated data.
2. Normalizing activity measures to a full day *(Normalized):* As described by *Katapally and Muhajarine*.[9] The total minutes of daily physical activity are normalized to a researcher defined "full day", with the goal of equalizing the different intervals of measured wear time. A 12-hour day was chosen as the researcher defined "full day" as it was the wear time amount used for inclusion in the true data set. Specifically; this calculation multiplies the original activity minutes (total PA or MVPA minutes)

by the minutes in the analyst defined "full day" (in this case 12 hours or 720 minutes). This measure is then divided by the participant's total wear time to get the normalized activity measure, which is then used in all subsequent physical activity analysis. For example, a participant with 20 minutes of MVPA and 10 hours (600 minutes) of wear time would have (20*720) / 600 = 24 minutes of MVPA after normalization to a 12-hour day.

3. Regression model adjustment for wear time *(Adjust for WT):* In this method no pre-processing of the physical activity data occurs. Minutes of physical activity (total PA or MVPA minutes) are used in the regression model and average wear time, averaged across all days of wear, is included as a covariate in the regression model.
4. Residualizing physical activity *(Residualized):* This correction is implemented by regressing week level physical activity minutes (total PA or MVPA minutes) on cumulative wear. Residuals from this model, inflated by the mean predicted value, are then used as the new, corrected, measure of physical activity. Residuals are inflated by the mean predicted value for ease of interpretation.
5. Random slope imputation *(RS)*: As described by Xu et al.,[18] this correction fits a linear mixed effects regression model of day level physical activity minutes (total PA or MVPA minutes) on day level wear time as the predictor variable. A random effect for both intercept and slope is included, resulting in a slope estimate for each individual ($\hat{\beta}_i$). This subject specific slope is then used to impute to an analyst defined "full day" (in this case 12 hours or 720 minutes) for all participants with less than a full day of wear by adding $\hat{\beta}_i$ x (720 – wear time) to the observed total physical

activity minutes to get the updated activity measure which is used in all subsequent physical activity analysis.

6. Multiple imputation with a zero inflated binomial log normal distribution *(MI):* A multiple imputation technique that specifies a mixture of a zero-inflated Poisson and Log normal distribution to specify the missingness. This method is implemented on minute level activity data using an R program (*accelmissing*) that was developed specifically for this use.[17]

For methods 2, 4, and 5; the wear time correction was applied to the day level PA data before aggregating to the week level. For method 6 the wear time correction was applied to the minute level PA data before aggregating to the week level.

Statistical Analysis

Descriptive statistics of the hours per week of total activity and minutes per week of MVPA were calculated in the true data and for each correction method in the simulated data (with the exception of method 3, adjusting for wear time, which does not change the activity data estimates). The mean was calculated separately in each of the 100 simulated data sets, the mean (*mean*) and standard deviation (*simulation SD*) of these 100 means was then reported in addition to the average standard deviation across the 100 data sets (*average SD*). Lastly, we calculated the correction bias as the difference between the true activity and the corrected activity.

To assess the correction potential of the various strategies we used separate linear regression models to assess the association between average week level PA (independent variable) and an outcome variable known to be associated with PA (BMI). Models were run separately using the true data with no correction and using the simulated data with each correction technique. Models adjusted for standard potential confounders (age, ethnicity, education, smoking status, alcohol use, breast cancer stage, and progesterone receptor status). In addition, correction method 3 *(regression model adjustment for WT)* also included the daily average wear time (based on the simulated week) as a covariate in the regression model.

Correction potential of each method was quantified by calculating the relative efficiency of each method compared to the naïve model, and statistical coverage, as well as by comparing the estimate ($\hat{\beta}_{PA}$) and p-values from the true data with that from the simulated data after each correction (model bias). Relative efficiency was calculated by taking the ratio of the mean-squared error (MSE) between the tested correction method and the uncorrected naïve method. Relative efficiency was calculated in comparison to the naïve method as MSE is calculated as the squared difference between the corrected estimate and the true data estimate, averaged across the simulations. Coverage was calculated as the proportion of simulation iterations for which the null hypothesis was rejected, with the estimate in the same direction as the true data, in each of the 100 simulated data sets, using the true data model's significance level as the alpha. Relative efficiency and coverage are displayed graphically by plotting a bar-graph of the relative efficiency/coverage produced by each correction method. Separate graphs are displayed for total physical activity and MVPA.

Regression models were run separately for each of the 100 simulated data sets and outcome parameters were averaged across the 100 data sets.

Results

The full RFH cohort had 333 subjects with an average of 10.8 (SD=4.1) wear days per person, and 10.2 (SD=5.7) hours per day of wear. The *true* data set, which included only days with ≥ 12 hours of wear, included 328 subjects with an average of 6.4 (SD=1.9) wear days per person, and 14.4 (SD=1.5) hours per day of wear making up the true data set. Across the 100 pseudo-simulated datasets, consisting of the 328 subjects, average device wear was 12.5 hours/day (average SD=4.2, simulation SD=0.02).

The distribution of weekly average min/day of total physical activity and MVPA in the true data, and in the simulated data with each wear time correction, is shown in **Table 2.1.** In comparison to the true data, the simulated data with no correction applied (*naïve*) underestimated total activity by an average of 41.58 min/day and MVPA by an average of 2.68 min/day. *Normalized* activity measures resulted in estimates of mean total activity and MVPA that were farthest from the true data, underestimating total activity and MVPA by an average of 49.26 min/day and 2.92 min/day respectively. In addition, normalization had the largest variation between simulations for MVPA (simulation SD = 0.47 min/day). *Residualized* activity, provides average estimates that are identical to the uncorrected data, but with slightly lower average standard deviation. *Random slope imputation* also provided average estimates roughly identical to the uncorrected data, but with a slightly larger average standard deviation. Random slope imputation also resulted in the largest variation between simulations for total PA and second largest for MVPA (simulation SD = 6.04 and 0.44). The *multiple imputation* technique resulted in estimates that were the second most closely matched to the true data, behind normalization, underestimating total activity and MVPA by an average of 14.55 min/day and 1.68 min/day respectively. The imputation technique also resulted in the lowest variation in total activity estimates across simulations (simulation SD = 0.84) although this same trend was not true for MVPA.

Table 2.1: Comparison of activity estimates: True data and simulated data with corrections applied.

	Total Physical Activity (min/day)				MVPA (Min/Day)			
Method	***Mean***	***Average SD***	***Sim SD***	**Mean Difference (Corrected-True)**	***Mean***	***Average SD***	***Sim SD***	**Mean Difference (Corrected -True)**
True Data (n=328)	326.74	83.97	--	--	20.24	18.40	--	--
Simulated Data								
1) Naïve	285.16	82.58	1.08	-41.58	17.56	16.35	0.17	-2.68
2) Normalized	277.48	73.76	1.25	-49.26	17.32	18.07	0.47	-2.92
4) Residualized	285.16	79.02	1.08	-41.58	17.56	16.23	0.17	-2.68
5) Random slope imputation	286.01	88.65	6.04	-40.73	17.63	17.67	0.44	-2.61
6) Multiple imputation	312.19	76.10	0.84	-14.55	18.56	16.35	0.20	-1.68

Numerical results of the comparison of regression model output for each correction methods are presented in **Table 2.2** while **Figures 2.2 to 2.5** present the corresponding graphical representation. As noted previously, relative efficiency was calculated as the ratio of MSE from the correction method versus that of the naïve method, thus lower values indicate better performance. Coverage was calculated as the proportion of times the null hypothesis was rejected, with the estimate in the same direction as the true data using the true data model's significance level as the alpha, thus higher values indicate better performance.

As shown in Table 2.2, comparison of the estimates for regression models of activity (total PA or MVPA) on BMI reveal differences from the true value that range from a 2% to 15% difference. For total PA, normalization and adjusting for wear time provided estimates closest to the true value (5% and 2% below the true value), however these corrections also resulted in the largest standard errors for the estimate. Conversely, for MVPA, normalization provided MVPA on BMI estimates among the farthest from the true value (11% below the true value) but resulted in the lowest standard error of the estimate (SE=0.94). Residualization resulted in estimates and standard errors equivalent to no correction, for both total PA and MVPA models. For total PA on BMI, random slope imputation provided estimates furthest from the true value (15% below the

Table 2.2: Comparison of regression model output: True data and simulated data with corrections applied.

	Method	*Estimate*	*Estimate (SD)*	*% Estimation Bias*	*SE of estimate*	*SE of estimate (SD)*	*Relative Efficiency*	*Percent Coverage*
Total Physical Activity (hr/day)	*Original Data*	*-0.53*	--	--	*0.20*	--	--	--
	1) Naïve	-0.48	0.10	-10%	0.21	0.006	1	25
	2) Normalized	-0.51	0.08	-5%	0.23	0.005	0.5	8
	3) Adjust for wear time	-0.52	0.05	-2%	0.23	0.003	0.2	0
	4) Residualized	-0.47	0.09	-11%	0.22	0.005	0.9	13
	5) Random slope imputation	-0.45	0.08	-15%	0.19	0.005	1.0	27
	6) Multiple imputation	-0.59	0.06	10%	0.22	0.004	0.5	45
MVPA (hr/day)	*Original Data*	*-3.67*	--	--	*0.91*	--	--	--
	1) Naïve	-4.02	0.23	9%	1.03	0.022	1	23
	2) Normalized	-3.25	0.63	-11%	0.94	0.088	3.3	9
	3) Adjust for wear time	-3.99	0.20	8%	1.04	0.021	0.8	10
	4) Residualized	-3.99	0.21	9%	1.05	0.022	0.8	10
	5) Random slope imputation	-3.74	0.19	2%	0.96	0.021	0.2	22
	6) Multiple imputation	-4.07	0.21	11%	1.03	0.021	1.2	30

true value) but with the smallest standard error of the estimate (SE=0.19). For MVPA on BMI, random slope imputation provided estimates closest to the true value (2% above the true value) and with the second smallest standard error of the estimate (SE=0.96). For total PA on BMI multiple imputation had similar bias and standard errors as no correction (10% bias, SE=0.22), but was the only correction to result in an estimate that was larger than the true value.

Comparison of relative efficiency in total physical activity models (Figure 2.3) illustrates that adjusting for wear time performed the best (RE=0.2), followed by normalization and multiple imputation (RE=0.5), while the relative efficiency of residualization and random slope imputation was similar to no correction (RE=0.9 and RE=1). In MVPA models (Figure 2.3) random slope normalization had the best relative efficiency (RE=0.2) while normalization performed the worst (RE=3.3) and the others performed similarly to no correction.

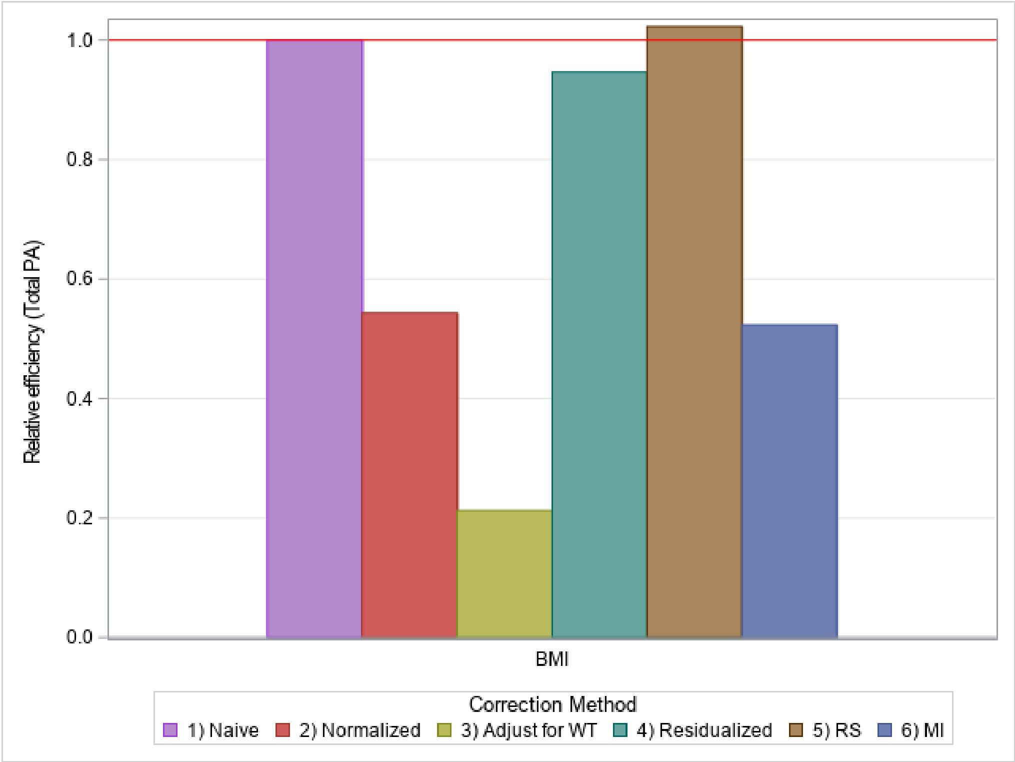

Figure 2.2: Relative efficiency, compared to the naïve model, of different correction methods in estimating the total physical activity coefficient.

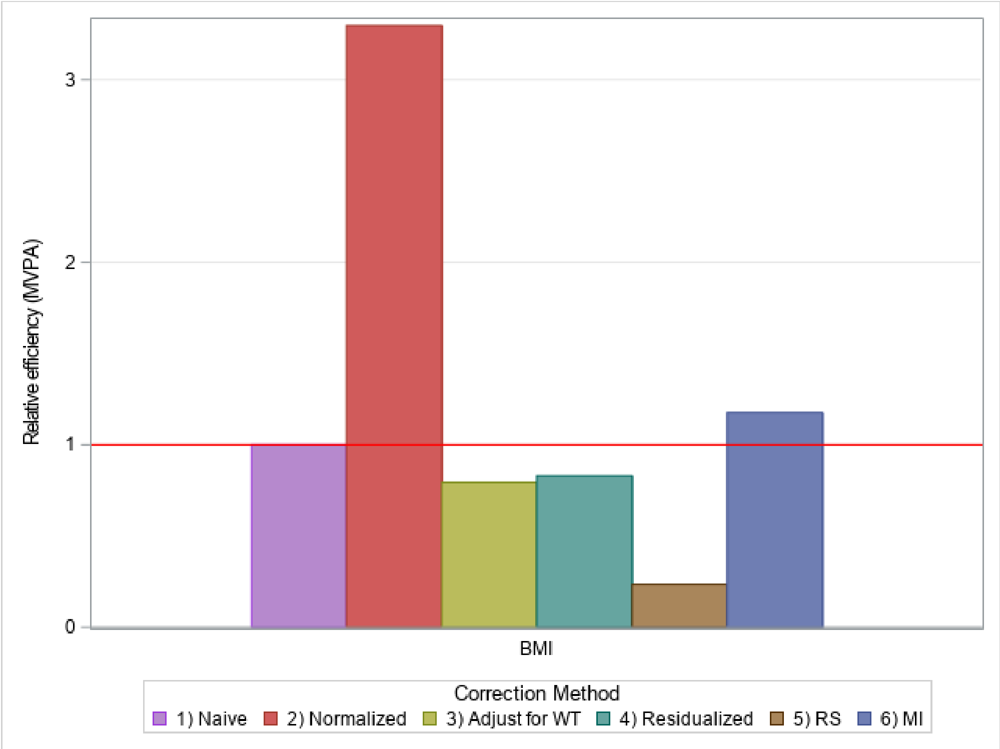

Figure 2.3: Relative efficiency, compared to the naïve model, of different correction methods in estimating the MVPA coefficient.

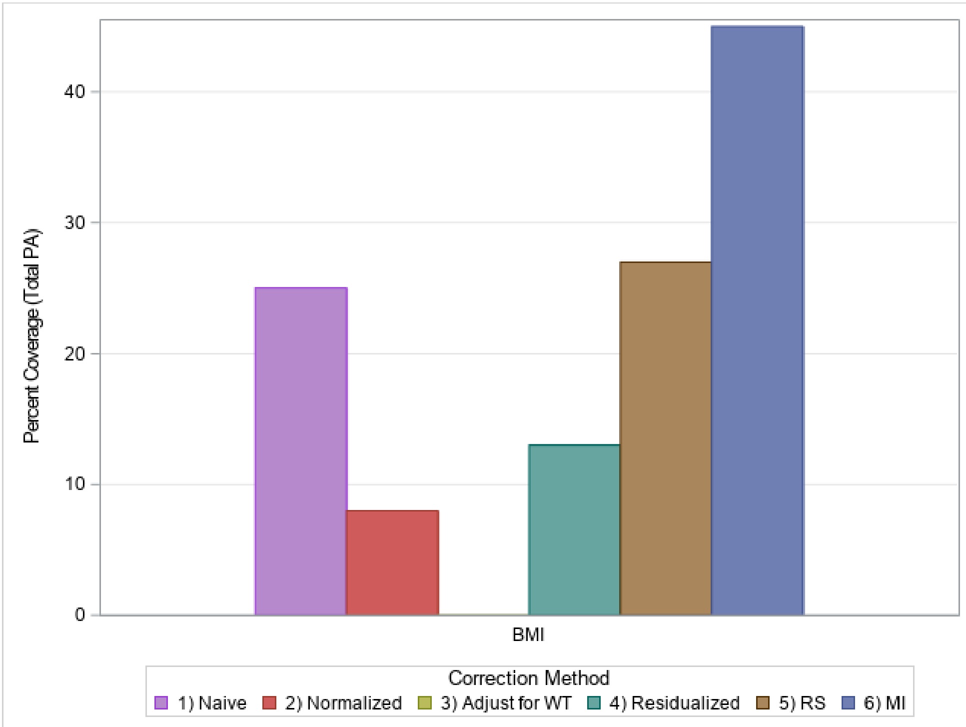

Figure 2.4: Comparison of coverage for estimating the significance of the total physical activity coefficient.

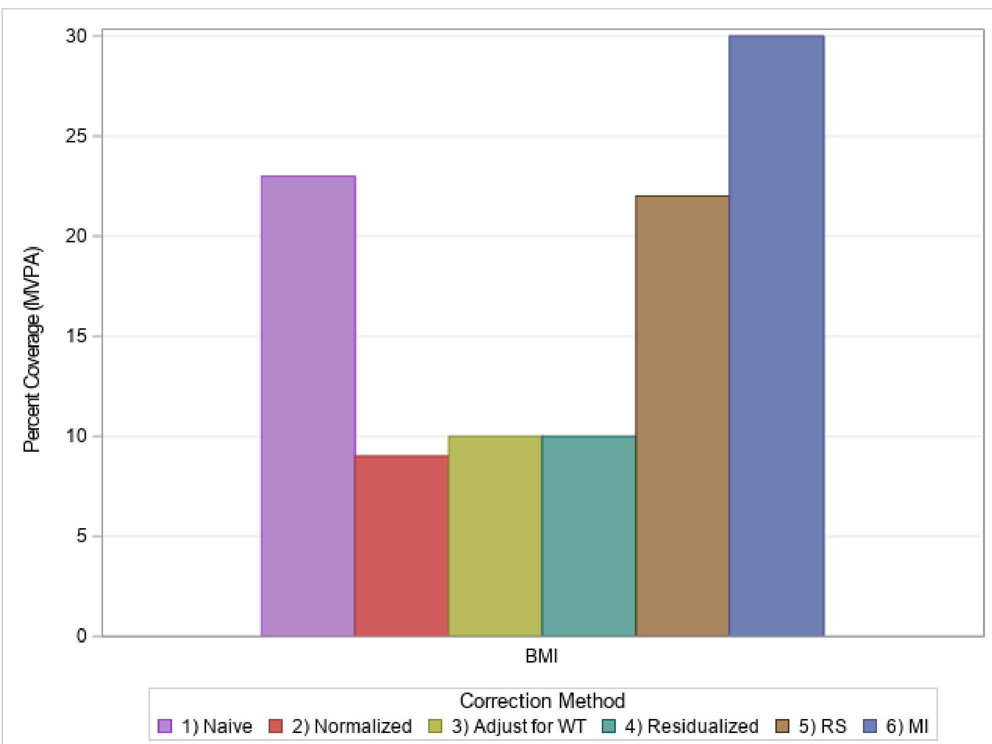

Figure 2.5: Comparison of coverage for estimating the significance of the MVPA coefficient.

Performance with regard to percent coverage (Figure 2.4) was consistent between total activity and MVPA models. Multiple imputation correction had the greatest percent coverage, followed by random slope normalization, which was similar to uncorrected data. While residualization, adjusting for wear time, and normalization all had coverage much lower than uncorrected data.

Discussion

In this study we used a pseudo simulation, based on generating real-world missing data patterns, to compare the efficacy and practical difference of 6 techniques used to account for missing accelerometer wear time. Quantifying and comparing the effectiveness of wear time correction techniques is important as it is a critical step towards uniform practice for physical activity analyses. Specifically, this study examined wear time corrections for use when physical activity is the independent variable of interest and day level physical activity must be aggregated to the week level.

We observed that the correction providing the greatest precision (relative efficiency) and least bias was not consistent between physical activity models (total activity or MVPA*).* For total PA, adjusting for wear time, arguably the most commonly used correction, had the least bias and the greatest relative efficiency, however had high standard errors and zero percent coverage. Also, for total PA, Random slope imputation had the largest bias and a relative efficiency equivalent to no correction however achieved low standard errors and relatively high percent coverage. Lastly with regard to total PA, multiple imputation had bias equivalent to no correction but good relative efficiency and the greatest percent coverage. For MVPA, adjusting for wear time and residualization performed equivalent to no correction but with much a lower percent coverage. Random slope imputation had the least bias and best relative efficiency but had only moderate coverage, equivalent to no correction. While multiple imputation had bias and precision slightly worse than no correction but did achieve higher coverage.

Adjusting for wear time is arguably the most common correction applied to physical activity research and while it performed well for bias and precision in the total PA model, it performed only equivalent to no correction in MVPA models and consistently achieved much lower coverage. Therefore, applying no correction appears to be a better alternative than adjusting for wear time.

Random slope imputation and multiple imputation appear to perform the best overall. Random slope imputation resulted in very high precision and low bias in the case of MVPA, moderate precision and bias in the case of total activity and good coverage in both cases. Another strength of random slope imputation is that it was also shown by Xu et al. to be a good option for use when physical activity is the dependent variable of interest,[18] thus providing a correction that is conducive to uniform practice in physical activity analyses (i.e. regardless of whether activity is the independent or dependent variable). A limitation of random slope imputation is that it is dependent on selection of an analyst-defined full wear day. This study used 12 hours as the full day as this was the minimum number of hours selected for inclusion into the true data set. However, the number of hours in the 'true' data is not knowledge that researchers with a free-living data set would know. Multiple imputation was also a viable correction as it resulted in the highest coverage for both total activity and MVPA. The multiple imputation approach also has the advantage of using a zero-inflated Poisson and Log-normal distribution to specify missingness and thus is more precisely tailored to the patterns of accelerometer missingness[17]; additionally we found that it produced more accurate average estimates of physical activity. However, a practical disadvantage is that this multiple imputation approach uses minute-level data (a major computational drawback in large observational studies).

There are limitations inherent to the use of a simulation, which relies on the assumption that the simulated data set is an accurate representation of what the data would be if those who wore their accelerometer all day had been less compliant. This limitation is greatly diminished by the use of a pseudo simulation, rather than a standard simulation, as pseudo simulations use actual data from similar participants to make these assumptions. At the same time, the use of a postmenopausal breast cancer survivorship population as well as the use of hip worn accelerometers with an "awake time" wear protocol (rather than 24-hour wear) may have led to a pattern of missingness different from what would have been seen in a different population with a different accelerometer wear protocol. In addition, RFH had a strict wear criterion for entry into the study and obtained re-wears for any participants who did not achieve at least 10 hours per day for 5 days. This is a strength of the study as the "true data" is representative of the entire sample rather than coming from just the few people with large wear. However, this is also a weakness as missingness patterns may be different in groups who are not compliant with this stringent re-wear criteria. Notably, these limitations are mitigated as other studies have found similar missingness patterns to the one used for our simulation.[22,23] Another potential limitation is that it is common practice in physical activity research to remove all days with less than a specified amount of wear from the analytic sample.[24,25] We were not able to test removal of days with less than a set number of hours as it would essentially undo the pseudo simulation, leaving only days with a small amount of wear removed, thus making any outcomes look more like the true data then would occur in a free-living situation. This is not a major limitation as a goal of this research was to identify a wear time correction that reduced the need to omit days with insufficient wear, thus increasing power and lowering participant burden to wear the device for extended periods.

In our population of older (postmenopausal) female cancer survivors, random slope imputation appears to be a viable option given its ease of use and good relative performance. While a future project should seek to further compare the random slope imputation and multiple imputation wear time correction techniques under various circumstances, this pseudo simulation approach provides a paradigm for testing correction methods and choosing the one that is best suited for each application and population.

In summary, this study provides a comparison of wear time correction techniques for use when physical activity is the independent variable of interest and day level physical activity must be aggregated to the week level. This adds to the literature for which there is only validation when physical activity is the dependent variable. Having a wear time correction validated in multiple analytic situations will allow for the standardization of techniques used in physical activity analyses and reduces the need to discard data with low wear. Our results indicate that use of a random slope imputation or accelerometer specific multiple imputation could help to negate the error, due to missing wear time, that is inherent in the use of accelerometers.

** Chapter 2 is currently being prepared for submission for the publication of the material. Co-authors include Selene Xu, Suneeta Godbole, Dr. Ruth Patterson, Dr. Jacqueline Kerr, Dr. Sheri Hartman, Dr. Caroline Thompson, and Dr. Loki Natarajan. The dissertation author was the primary investigator and author of this material.*

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CHAPTER 3:

Continuous, Objective Measurement of Physical Activity During Chemotherapy for Breast Cancer: The Activity in Treatment Pilot Study

Sandahl H. Nelson, Lauren S. Weiner, Loki Natarajan, Barbara A. Parker, Ruth E. Patterson, Sheri J. Hartman

ABSTRACT

Purpose: To assess patterns of objectively measured physical activity in women undergoing chemotherapy for breast cancer and identify predictors of these patterns.

Methods: Thirty-two women enrolled in the Activity in Treatment observational pilot study prior to starting chemotherapy. All women were given a Fitbit to wear throughout chemotherapy. Restricted cubic splines were used to assess non-linear patterns of Fitbit measured total physical activity (TPA) and moderate to vigorous physical activity (MVPA) throughout the duration of chemotherapy treatment (mean of 17 weeks, SD=6.3). Mixed effects regression models were used to assess the rate of decline. Regression of subject level random slope were used to assess predictors of the rate of decline in PA on participant characteristics, cancer characteristics, and self-reported physical and mental functioning.

Results: MVPA declined linearly at a mean of 1.4 min/day ($p=0.002$) for every 10% of the duration of chemotherapy, while total activity declined linearly at an average of 13.4 min/day ($p=0.0007$) for every 10% of chemotherapy, until around half way through chemotherapy at which point activity rates leveled off. Having HER+ receptor status was associated with a greater rate of decline in MVPA, $\beta=13.3$, $p=0.04$.

Conclusion: Much of the reduced physical activity level seen among breast cancer survivors looks to occur during the first half of a course of chemotherapy. It appears that interventions to target physical activity should target this early decline in activity levels.

Introduction

Over 3.1 million women are currently living with a diagnosis of breast cancer in the United States (US), representing 41% of all female cancer survivors.[1] The increased breast cancer survival rate has necessitated a shift in cancer care towards enabling patients to improve their quality-of-life during and after treatment. Dependent on the stage, some 40-75% of women diagnosed with breast cancer receive chemotherapy[1] which is often associated with negative side effects such as fatigue, nausea, disturbed sleep, decreased activity, and weight gain.[2-4] Data from animal and human studies indicate that physical activity after a diagnosis of breast cancer may counteract some of these negative effects, thus improving quality of life for breast cancer survivors.[5-10]

Despite many potential benefits of engaging in physical activity during breast cancer treatment, it appears that activity levels typically decline throughout treatment.[11-15] Much of the existing research on how physical activity changes with breast cancer has focused on physical activity levels in the period following treatment. These studies have found activity levels to be below that of healthy controls and well below recommended levels.[16-20] Numerous observational studies have examined patterns of physical activity during active treatment for breast cancer.[11-15,21-23] However, to our knowledge, all studies but one relied on self-reported activity levels and therefore only able captured periodic, often retrospective, snap shots of activity. Despite these limitations, the majority of studies agree that physical activity decreases from before to after treatment[11-15] and that the decrease is greater in women who receive chemotherapy as part of treatment.[11,15,22] Additional factors have been assessed as predictors of this decline, including age and obesity, but findings are mixed.[11,13-15] Randomized controlled trials of physical activity during treatment for breast cancer indicate significant positive effects, including improved sleep quality,[5] fatigue improvement,[8] and increased disease free survival.[6,7] In addition, evidence from animal studies indicate that physical activity during treatment may increase the efficacy of chemotherapy.[24,25] Therefore, understanding the patterns and predictors of physical activity during chemotherapy can have a significant public health impact by facilitating interventionists' understanding of key points in the process in which to intervene, and by helping clinicians assess when their patients are most likely to need extra motivation to stay active.

In the Activity in Treatment (ACT) pilot study, we assessed daily physical activity levels using objective measurement throughout the patient's chemotherapy treatments. We recruited women just before initiation of chemotherapy for breast cancer and all women were given a wrist worn activity tracker (a Fitbit Charge HR) to wear throughout the duration of their treatment. The daily activity data, along with chemotherapy associated medical records, were gathered to assess natural trends in physical activity throughout chemotherapy and assess health and participant characteristics associated with changes in physical activity.

The aim of this study is to increase our understanding of free-living patterns of physical activity during chemotherapy for breast cancer and to assess correlates of these patterns in physical activity.

Building on the evidence that physical activity is beneficial during chemotherapy,[10] yet is decreased in breast cancer survivors,[16-20] this in-depth data will provide a new perspective on the patterns of activity levels. It will also help to identify if there are critical times in which to intervene to prevent physical activity declines, thereby helping to inform the development of disseminable physical activity programs that can shape guidelines for providers to help their patients stay physically active during this important time.

Methods

Study Design

This was a longitudinal pilot study that recruited breast cancer patients who were scheduled to have chemotherapy at a UC San Diego clinic. Participants were recruited prior to starting chemotherapy via oncologist referrals and flyers posted in the oncologists' waiting room. Flyers directed potential participants to contact the research team by telephone or email and/or potentially eligible participants were approached by their oncologist to determine interest and were then contacted via telephone by study staff. All potential participants were screened by telephone for eligibility based on the following inclusion criteria: (1) diagnosed with breast cancer, (2) scheduled to receive chemotherapy, but had not yet started, (3) receiving chemotherapy at a UCSD clinic, (4) willingness to wear the Fitbit monitor throughout their course of chemotherapy, (5) access to a computer or Bluetooth enabled phone/tablet to upload the Fitbit data, (6) able to read and communicate in English, (7) Age 21 to 85 years old, and (8) No serious physical limitations that greatly limited mobility.

Interested and eligible participants attended a single study visit at the start of the study, prior to initiation of their chemotherapy. At this visit participants were provided a wrist worn activity tracker, the Fitbit Charge HR, and were instructed on how to wear and upload (synch) the Fitbit data on a computer or mobile device. Participants were asked to wear the Fitbit for 24 hours a day throughout chemotherapy and to sync it with the Fitbit mobile app or website at least once a week. Participants were not asked to alter their exercise in any way. Participants also completed computerized Patient-Reported Outcomes Measurement Information System (PROMIS) questionnaires. At study completion, data from electronic medical records were collected including stage and cancer characteristics at diagnosis, type of surgery, chemotherapy regimen, and date of each infusion visit. The study was approved by the UC San Diego Institutional Review Board and all participants provided written informed consent.

Measures

Fitbit Measured Physical Activity

Physical activity data was collected through the Fitbit Charge HR, an accelerometer-based activity meter that collects data on intensity of physical activity at the minute level. The Fitbit Charge HR has begun to be validated against the Actigraph GT3X and has shown strong correlation[26] and although step counts appear to provide poor agreement, agreement in regard to MVPA is strong.[27] The Fitbit is watch sized, provides a digital clock, is wrist worn, and holds 20 days of physical activity data. Fitbit data (physical activity and heart rate) was accessed through Fitabase, a web-based database program that collects physical activity, heart rate, and sleep data from the Fitbit cloud. Study staff monitored Fitabase to ensure that the Fitbit was being synced and charged. Participants were contacted by study staff if they had not synced for at least one week or if battery charge was low.

Fitbit's proprietary algorithm classifies the types of activity over a 24-hour day, with each minute classified as being asleep, sedentary or in light, moderate, or vigorous activity. Activity level by minute was downloaded and cleaned using R[28] to calculate daily total physical activity minutes (TPA), moderate to vigorous physical activity minutes (MVPA), and total non-sleep wear minutes. Non-wear time was determined by the lack of heart rate and activity (steps or intensity) at any given minute. All days are considered a "valid day" if there was any wear recorded (defined as > 5 minutes of wear). This 5-minute threshold for a valid Fitbit wear day was used to avoid recording days where the Fitbit had simply been picked up and moved from one place to another while, at the same time, avoiding excluding days where the participant had purposefully worn the Fitbit. Our analyses used an inverse wear time weighting, which has been validated to account for missing wear without excluding days based on minimum wear hours in a day.[29]

Chemotherapy

Participants were asked to wear the Fitbit throughout their chemotherapy. For this study, we defined chemotherapy time in terms of the original chemotherapy plan. Participants who, after completing or stopping their original planned chemotherapy, were switched to a different chemotherapy regime and given a new chemotherapy plan, were considered finished with the original chemotherapy plan for the purposes of our analyses. The first day of chemotherapy was defined as the first day of infusions and the final day was defined as 14 days after the last infusion of the original chemotherapy plan. Fourteen days was chosen because it was the mean length of time between infusions.

Other Measures

Medical charts were abstracted to obtain information regarding cancer diagnosis and treatment (cancer stage at diagnosis, receptor status, date of each infusion), height and weight. Baseline questionnaires were used to collect demographic data as well as self-reported cognitive and physical functioning. PROMIS questionnaires were used to measure the self-reported cognitive and physical functioning. These measures assess patient-perceived abilities and problems in the past 7 days. Higher scores represent greater ability. The scores are standardized with a mean of 50 and a SD of 10.

Data Analyses

Descriptive statistics (mean/SD or n/%) were calculated for demographics, self-reported functioning, and cancer related variables. In addition, we calculated the mean and standard deviation (SD) for the number of days participants wore the Fitbit as well as the average percentage of chemotherapy days with Fitbit wear. Lastly, we (1) calculated the mean and SD for each participant's average minutes/day of MVPA, TPA, and hours/day of non-sleep wear overall; and (2) calculated these values during the time pertaining to 0-10%, 45-55%, and 90-100% of chemotherapy completed. Given variation in chemotherapy lengths among participants, the percentage of treatment that had been completed at each day (percentage chemotherapy completed) was used as the time variable throughout this analysis to standardize the time axis, with all statistical analyses controlling for the total number of chemotherapy infusions. Patterns of physical activity were examined graphically by plotting the average day level physical activity (MVPA or TPA) by percentage of chemotherapy completed, with a rolling average of the physical activity overlaid as a line to help visualize trend.

Statistical Analysis

Restricted cubic splines (RCS) were used to model patterns of change in physical activity (MVPA and TPA) throughout chemotherapy (modeled as the percentage of chemotherapy completed) while allowing for non-linearity. RCS models included 3 knots as determined by QIC comparison. The 3 knots were located at prespecified locations according to the percentiles of the distribution of percentage of chemotherapy completion, the 5^{th}, 50^{th}, and 95^{th} percentiles.[30] The restricted cubic spline model was carried out using mixed effects regression with a subject level random intercept and slope. A test for non-linearity was carried out by comparing the log likelihoods of the model containing the knots with the linear model. Restricted cubic splines were carried out using PROC GLIMMIX, SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA). Interpretation of non-linear models was carried out graphically by plotting predicted physical activity (MVPA or TPA), based on the RCS model, on the y axis by percentage of chemotherapy completed on the x axis.

After visual inspection of the RCS model, we assessed the linear change in physical activity throughout chemotherapy (modeled as the percentage of chemotherapy completed) for the visually ascertained linear range (0-60% for MVPA and 0-50% for TPA) using linear mixed effects models with a subject level random intercept and slope on percentage of chemotherapy completed. All models control for the confounding effects of total infusion count, cancer stage, receptor status, education, BMI, and age. All models account for wear time using inverse wear time weighting[29] and use an unstructured covariance structure.

We assessed 7 possible predictors of the rate of physical activity change; participant characteristics (age, BMI), cancer related variables (receptor status, cancer stage, mastectomy), and baseline self-reported functioning (cognitive and physical). Predictors of the rate of physical activity change were assessed by first determining the subject specific slope. The slopes were determined using a linear mixed effects model of the 2 physical activity measures (separately) on percentage of chemotherapy completed, with a subject level random intercept and slope, controlling for total infusion count and accounting for wear time using inverse wear time weighting. The mixed effects model was carried out on only the portion of chemotherapy determined to have a linear decline in activity based on visual assessment of the restricted cubic spline model (0-60% for MVPA and 0-50% for TPA). We then regressed the subject level slope on each of 7 possible predictors: age, BMI, receptor status, cancer stage, mastectomy and baseline self-reported cognitive and physical functioning.

Results

Study Population

Eighty-one women were screened by telephone for eligibility. Of these, 33 were eligible and 32 completed a baseline visit. Ineligibility reasons included: already started chemotherapy (n=19), change in treatment plan or no longer receiving chemotherapy (n=12), not receiving chemotherapy at UCSD (n=5), uncomfortable reading/communicating in English (n=3), and not interested/unable to comply with study procedures (n=42).

Baseline characteristics of the 32 study participants are outlined in Table 3.1. Participants were on average 50 years old, had a BMI of 28, and reported roughly average self-reported cognitive and physical functioning. The majority of participants had stage II cancer and received a lumpectomy. The participants received, a mean of 10 chemotherapy infusions and had a mean chemotherapy duration of 17 weeks.

Physical Activity Trends

Table 3.2 provides the distribution of Fitbit wear and average physical activity (min/day of TPA and MVPA) overall and at segments of chemotherapy corresponding to 0-10%, 45-55%, and 90-100% of chemotherapy completed. On average, women wore the Fitbit for 84% (SD=20.1) of their chemotherapy days and wore the Fitbit on average 13 (2.7) waking hour/day. Participants averaged 11 (9.4) minutes/day of MVPA and 189 minutes/day (77.2), or 3.2 hour/day, of total activity.

Figures 3.1 and 3.2, provide a graphical representation of average day level physical activity by percentage of chemotherapy completed. Figure 3.1 shows that MVPA declines throughout chemotherapy while, Figure 3.2, shows that total physical activity declines until about half way

Table 3.1: Participant characteristics in a sample of breast cancer patients (n=32)

Variable	mean (SD) or n/%
Demographics	
Age	49.6 (10.72)
BMI	27.5 (6.03)
White	25 / 78.1%
Latina	5 / 15.6%
Education (% college graduates)	20 / 62.5%
Married or living with partner	17 / 53.1%
Employed	22 / 68.8%
Self-reported functioning	
Cognitive	51.9 (10.92)
Physical	54.0 (6.11)
Cancer Characteristics	
Disease stage	
Stage I	5 / 15.6%
Stage II	19 / 59.4%
Stage III	6 / 18.8%
Stage IV	2 / 6.3%
Receptor type	
HER2+	9 / 28.1%
ER+ or PR+, HER2-	12 / 37.5%
Triple-negative (ER-, PR-, HER2-)	11 / 34.4%
Pathologically positive lymph nodes	18 / 58.1%
Mastectomy	9 / 28.1%
Infusion count	9.7 (6.02)
Chemo duration, weeks	17.3 (6.26)

Table 3.2: Physical activity and Fitbit wear distribution (n=32)

Variable	Mean (SD)
Days with Fitbit wear[¥]	102.5 (48.42)
Percent of chemo days with Fitbit wear	84.0 (20.10)
Chemotherapy Overall	
Fitbit wear hours/day[†]	12.9 (2.69)
MVPA min/day	10.5 (9.43)
Total PA min/day	189.1 (77.15)
*0-10% of chemotherapy**	
Fitbit wear hours/day[†]	13.9 (2.80)
MVPA min/day	15.2 (15.42)
Total PA min/day	203.5 (89.75)
*45-55% of chemotherapy**	
Fitbit wear hours/day[†]	12.4 (4.11)
MVPA min/day	9.7 (11.00)
Total PA min/day	183.8 (82.82)
*90-100% of chemotherapy**	
Fitbit wear hours/day[†]	12.8 (3.57)
MVPA min/day	7.2 (8.72)
Total PA min/day	172.4 (93.01)

¥ Days with > 5 min wear

† Non-sleep wear

*Distribution at proportion of chemotherapy completed

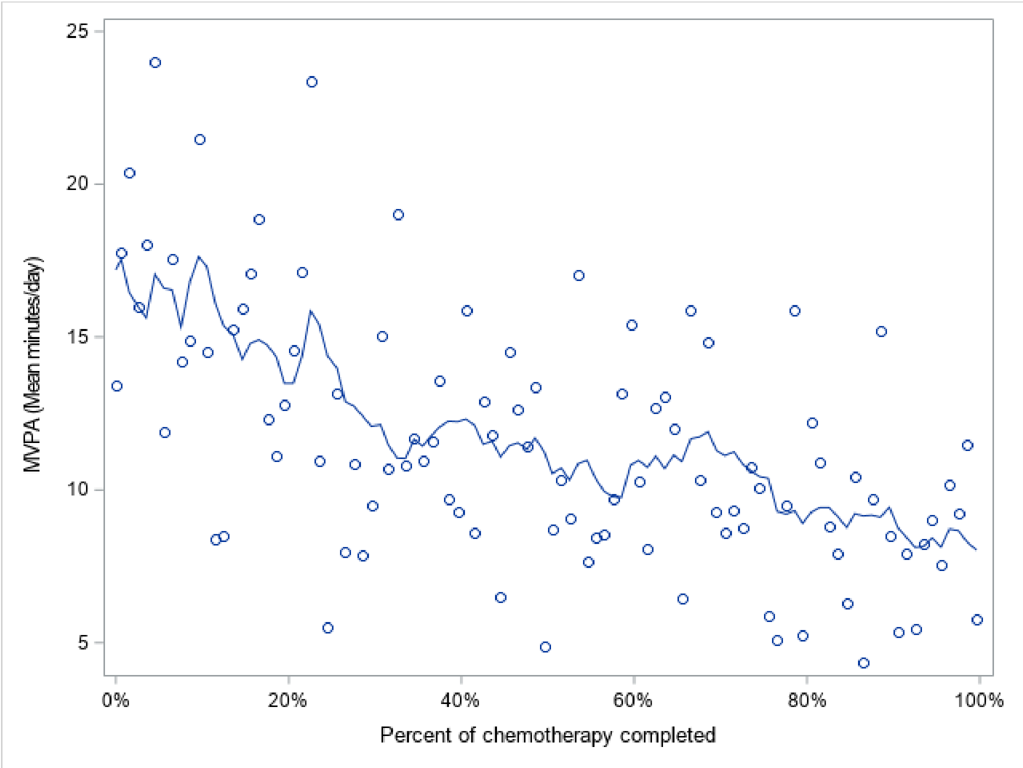

Figure 3.1: Distribution of MVPA by percent of chemotherapy with rolling average trend line, n=32

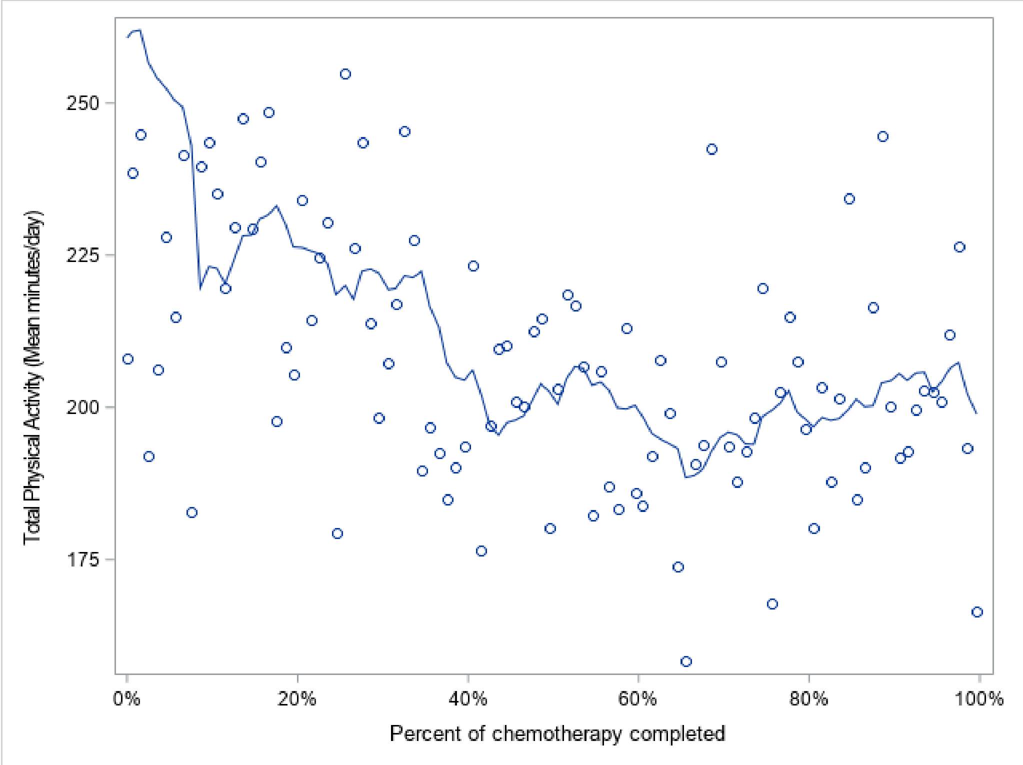

Figure 3.2: Distribution of Total Physical Activity by percent of chemotherapy with rolling average trend line, n=32

through chemotherapy and then levels off. Because these figures appear to suggest a tapering off in the decline in activity, we began our examination by assessing the significance of a non-linear association between activity and percentage of chemotherapy.

Non-linear analysis of activity by percentage of chemotherapy shows a significant non-linear association for both MVPA and TPA (both $p < 0.001$). Figures 3.3 and 3.4 provide graphical interpretation of the non-linear model. In Figure 3.3 we see that MVPA declines roughly linearly until around 60% of chemotherapy and then levels off. In Figure 3.4 we see that TPA declines until around the midpoint (50%) of chemotherapy and then rebounds slightly.

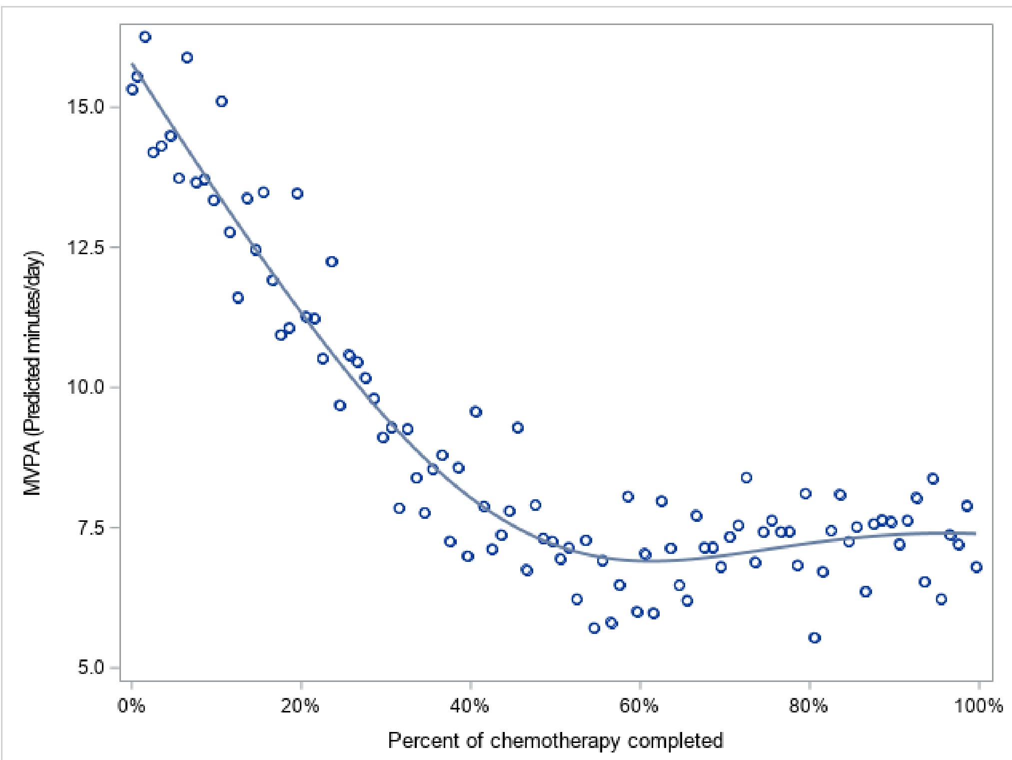

Figure 3.3: Non-linear association between percent of chemotherapy and MVPA, n=32

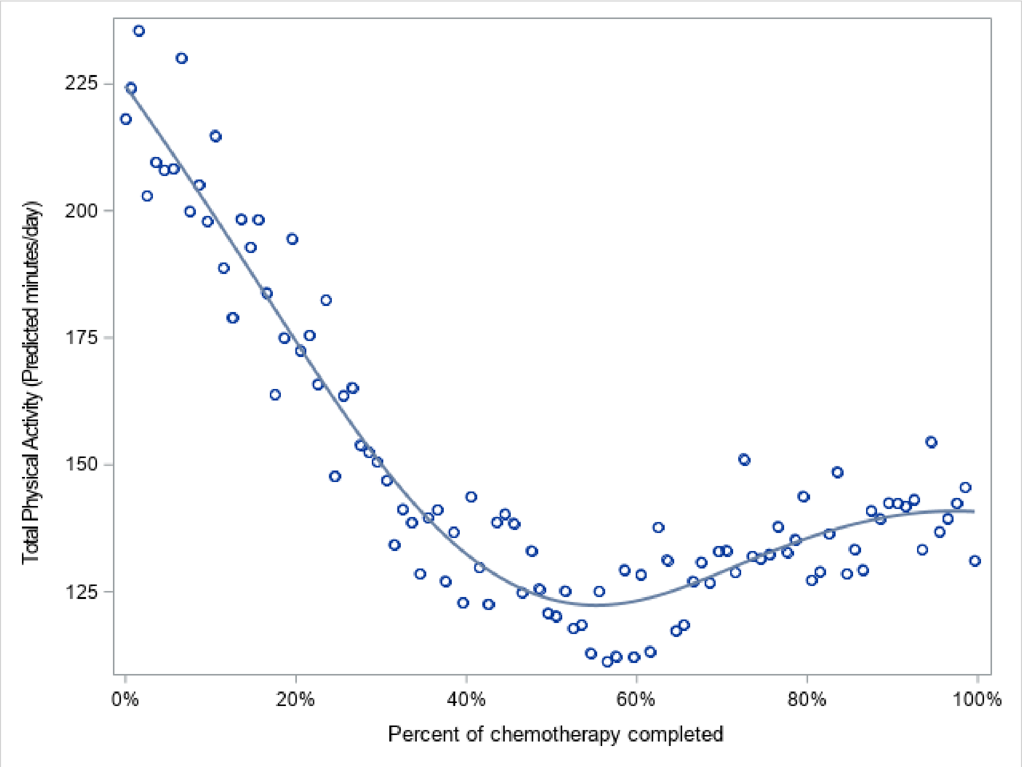

Figure 3.4: Non-linear association between percent of chemotherapy and total activity, n=32

Based on our non-linear analysis we carried out statistical analysis of the linear change in activity by percent of chemotherapy, during the portion of chemotherapy with a linear trend (0-60% for MVPA and 0-50% for TPA based on visual inspection of the non-linear analysis) Linear analysis shows a significant decrease in MVPA and TPA as chemotherapy progresses (β=-14.2, p=0.002 and β=-133.9, p=0.0007). This can be interpreted as a 1.42 minute/day decline in MVPA and a 13.39 minute/day decline in TPA for every 10% of chemotherapy that passes, up until physical activity decline plateaus, equating to a total decline of 8.5 minutes/day (1 hour/week) in MVPA and 67 minutes/day (7.8 hours/week) in TPA.

Predictors of Physical Activity

We assessed age, BMI, receptor status, cancer stage, mastectomy, and baseline self-reported cognitive & physical functioning as potential predictors in the rate of physical activity decline. We found no significant predictors for TPA, although BMI did trend towards greater declines in TPA (β=-7.9, p=0.09). For rate of decline in MVPA, receptor status was significant: those with a HER2+ receptor status had a significantly greater rate of decline then those with a HER2- and ER or PR+, or triple negative receptor status (β=13.3, p=0.04). However, when compared individually, the difference between HER2+ and those who were HER2- /ER+ or PR+ and between HER2+ and triple negative did not achieve significance (β=14.1, p=0.05 and β=12.5, p=0.09). This result is likely due to the relatively small sample size when split into 3 groups. No other variables were significant predictors for declines in MVPA, although age and BMI did trend towards greater declines in MVPA (β=-0.42, p=0.12 and β=-0.68, p=0.16).

Discussion

In this pilot study we assessed physical activity using daily objective measurement in 32 women throughout the duration of their course of chemotherapy for breast cancer. We observed a significant decline in MVPA and TPA from the start of chemotherapy until roughly half way through treatment. Equivalent to a decrease of 1 hour/week in MVPA and 8 hour/week in total activity. We also found that a HER2+ receptor status, greater age, and higher BMI were the strongest predictors of decline in MVPA.

To our knowledge, this is only the second study of physical activity during chemotherapy for breast cancer, outside of a physical activity intervention, to use an objective assessment of physical activity. To our knowledge, it is also the first to include an assessment of physical activity for the duration of a complete course of chemotherapy. The first study using objective measures[23] assessed only the first 14 days of chemotherapy and measured steps rather than minutes of activity as our study does. Despite these differences, their findings are consistent with ours as they also found a significant decrease in activity even in this short time.[23] Our findings are also consistent with the largest study to examine physical activity during treatment for breast cancer,[15] (n=19,696) which assessed retrospectively self-reported pre-diagnosis activity and activity at 6 months after diagnosis. Their study included all treatment types and found the greatest decrease in physical activity was among those who underwent chemotherapy. They reported a decrease in MVPA of around 2 hours/week for those who received chemotherapy and 1.6 hours/week for those who received chemotherapy and radiation. This finding was consistent with ours, although was larger than the decrease of 1 hour/week in MVPA that we observed based on our linear analysis. The difference is partially explained due to the previous study's comparison with pre-diagnosis activity levels which another study found to be higher than post-diagnosis/pre-treatment levels.[31] Another explanation for the discrepancy in magnitude of findings is the difference in measurement (self-report versus objective) because self-report physical activity is prone to poor recall or social desirability (ie, over-reporting of activity).[32] Our use of objective measures also expands upon their findings as these measures permitted daily measurement, allowing for the elucidation the timing of changes in physical activity levels during chemotherapy.

Several studies have reported that the greatest declines in physical activity were seen in those who received chemotherapy.[11,15,21] Our study focused on those receiving chemotherapy and, unlike these earlier studies, examined factors within this population that might signal an opportunity for increased intervention to thwart decline. We found that those with a HER2+ receptor status had significantly greater decline in MVPA, a result not seen in the only other study to examine this predictor.[15] This discrepancy may be due to the fact that our study was restricted to those receiving chemotherapy, and it might be only among those treated with chemotherapy that HER2 status predicts decline. It is also possibly explained by the use of specific chemotherapy in HER2 positive cancers.[33] We also found that increased age and BMI were associated with greater, although non-significant, decreases in MVPA, both of which are consistent with previous findings.[11,14,15]

Studies assessing activity levels in women only after the completion of treatment have found that physical activity in breast cancer survivors is below recommended levels[16,17,20,34] and below that of matched controls.[18,19] These previous studies report only small further decreases in activity following completion of treatment,[17,20] coupled with our findings, this suggests that the decline is happening during treatment.

There are several limitations to our study. As this was a pilot study, the chief limitation is the small sample size. Despite this, the long duration of daily measurements allowed us to assess significance of the decline in activity. The assessment of physical activity throughout chemotherapy is also limited by the fact that women undergo chemotherapy of varying lengths. We attempted to mitigate this by changing the time scale from days to percent of chemotherapy completed at each day. In this way we were able to avoid having extremes of time with only a few, potentially sicker, participants still completing their chemotherapy.

Another possible limitation is the use of a commercially available Fitbit to measure activity. Because the Fitbit provides the user immediate feedback on activity and steps taken, this might have resulted in women being more active than they otherwise would have been, potentially attenuating our findings. However, a previous trial found that a Fitbit alone did not significantly increase physical activity beyond that seen in controls.[35] A final limitation is the possibility that selection bias may have occurred because participants knew they would be provided a Fitbit. Consequently, women more interested in/accustomed to physical activity may have self-selected to participate. Previous research has shown that women with higher starting levels of activity have greater declines in activity during treatment,[15] thus our study may have seen greater declines than if no self-selection had occurred.

Despite limitations, using Fitbit to record activity offered considerable advantages. First is the strength of using an objective, versus self-report, measure to capture physical activity, thereby reducing possible bias due to recall or social desirability.[32] Second is the fact that, in addition to activity, the Fitbit monitors heart rate, making wear time more measurable. Lastly, by using the Fitbit, which has been designed to be small and attractive and acceptable for long term use, we were able to ask women to wear the device for the entirety of chemotherapy and achieve high compliance.

Given the WHO recommendation of 150 min/week of MVPA,[36] the decrease of 60 min/week of MVPA is alarming and is likely a large contributor to the low activity levels seen among breast cancer survivors. Therefore, these results indicate that interventions are needed early in chemotherapy to stem this decrease in activity. The next step, beyond replicating these findings in a larger cohort of patients, is to recruit women early enough to be able to objectively measure trends in activity starting prior to diagnosis and continuing into chemotherapy. This would expand our understanding of the decline in objectively measured physical activity and provide a greater understanding of when to intervene.

To our knowledge, this is the first study to undertake objective daily measurement of physical activity throughout the duration of chemotherapy for breast cancer. This protocol made it possible to examine patterns in activity and pinpoint the chemotherapy-related decline in physical activity, a critical finding that can aid development of interventions to counteract this drop in physical activity.

** Chapter 3 is currently being prepared for submission for the publication of the material. Co-authors include Lauren Weiner, Dr. Loki Natarajan, Dr. Barbara Parker, Dr. Ruth Patterson, and Dr. Sheri Hartman. The dissertation author was the primary investigator and author of this material.*

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DISCUSSION

Physical activity is associated with improved outcomes and quality of life in breast cancer survivors.[1,2] Although there is a growing body of research on physical activity in cancer survivors,[3] there remains a lack of standardization in how physical activity data is collected, analyzed, and interpreted.[4] At the same time, recent advances and market adoption of wearable activity monitors have made it possible to collect long term, continuous, objective data of patients rather than relying on snapshots of activity.[4,5]

The overarching theme of this dissertation is physical activity among breast cancer survivors, with a two-fold goal. First, we examine methodological issues in the collection and analysis of physical activity data within this population. Second, we aim to fill the gap in knowledge regarding free-living physical activity of patients undergoing chemotherapy for breast cancer using a commercially available activity tracker allowing for long term, continuous, collection of data.

Capturing Physical Activity Estimates

Historically, physical activity estimates have been assessed using participant self-report. However there has been a shift to objective measurement using accelerometers, which avoids the potential for bias in self-report, such as recall or social desirability.[6] Nonetheless, physical activity estimates captured using standard accelerometer cut-points may be insensitive, especially misclassifying older adults due to differences in perceived (relative) and measured (absolute) intensity.[7] Chapter 1, titled *Physical activity change in a randomized trial: comparison of measurement methods*, examined the agreement between self-report and standard cut-point accelerometry within the context of a randomized trial that promoted increased physical activity in postmenopausal breast cancer survivors. This chapter also examined a machine learning method for processing accelerometer data to provide estimates that would more readily account for perceived intensity while still avoiding biases associated with self-report. The context of a randomized trial allowed us to examine how these measurement methods compare cross-sectionally and how they capture change in activity after an intervention to increase physical activity.

In the comparison of baseline measures of MVPA, we found that self-report estimates were much higher than standard 1952[8] cutpoints. However, self-report estimates were closely matched with activity estimates from both machine learning and the 1041 accelerometry cut-points, the 1041 cutpoints being a newer threshold proposed to be more appropriate for older adults.[9] While all comparisons of the similarity between self-report and machine learning algorithms are novel, our findings regarding the similarity of self-report and 1041 cut-points are not consistent with what is generally reported in the literature. The Women's Health Study (WHS) found that 1041 cut-points produced *lower* estimates (than self-report) of the percent meeting recommended activity levels.[10] A second study out of Australia found that 1952 cut-points produced *higher* estimates than self-report.[11] The differences in these studies, both from each other and from our study, are likely explained by the difference in self-report measures that were used. Specifically, we used the GPAQ questionnaire while WHS and the Australian studies used study-specific questionnaires. Some of the differences may also be due to study eligibility criteria. For example, participants in the Australian study were only eligible if they reported low enough levels of activity. These differences spotlight the need to standardize self-report measures and are a compelling reminder that comparisons of study findings that use different self-report measures should be done cautiously.

We also found that self-report estimates showed large increases in physical activity among both the intervention and control group, while accelerometry-based methods (machine learning and cut-points) detected only modest increases in the intervention group and showed decreases among the control group. Previous studies reported a decreased correlation between self-report and cutpoint accelerometry following an intervention.[11] However, we had a novel finding that the correlation decreased significantly more within the control group than the intervention group. As the goal of randomized trials is often to detect a statistical difference in change, we also examined the sensitivity of each measure to detect this difference. We found that only the machine learning and 1952 cut-points provided sensitive enough measurements to detect a significant difference in physical activity change.

Machine learning did not produce the differential bias in change that self-report suffers from, was sensitive enough to detect a difference in change between groups, yet still produced estimates more closely aligned with the perceived intensity captured by self-report. Thus, we concluded that machine learning algorithms are a promising method for physical activity research. A large new cohort of cancer survivors is in the process of longitudinal data collection that includes accelerometry measures.[3] Therefore machine learning methods have considerable potential for better integration of findings from new data collected and previous self-report findings.

Analysis of Objective Physical Activity Estimates

This dissertation's inspection of methods used to capture physical activity estimates in chapter 1 highlights the bias associated with self-report measures and with objective measures due to different decision rules (e.g. cutpoints) used to process the raw data. However, another important area that can lead to bias in objective, accelerometer, measures is differences in device wear time. While studies can apply strict wear time criteria, there will likely still be some missing wear time, resulting in biased estimates as well as the discarding of low wear days, further reducing power and increasing participant burden. Chapter 2, titled *Accelerometer measured physical activity: Methods to account for missing wear*, examined statistical methods used to account for variation in wear time. Specifically, Chapter 2 used a pseudo simulation based on a cohort of postmenopausal breast cancer survivors to compare 6 different methods for dealing with wear time in the analysis of physical activity as the independent variable of interest.

We found that adjusting for wear time, arguably the most commonly used correction, had good relative efficiency compared to no correction, however this adjustment had poor coverage compared to the true data. Therefore, adjusting for wear time is a poor choice of correction when we wish to assess the association between physical activity and health outcomes while avoiding type II statistical errors. We found that random slope imputation, a novel method introduced by Xu et al.,[12] and a multiple imputation with zero inflated binomial log normal distribution, designed specifically for accelerometer data by Lee et al.,[13] provided the best coverage. We also found that random slope imputation had good relative efficiency and low bias for MVPA but not (comparably) for total activity; while multiple imputation had good relative efficiency and low bias for total activity but not MVPA.

It is worth noting that while these 2 methods performed the best, we observed little practical difference (regarding bias and efficiency) between doing nothing regarding wear time and applying one of these computationally heavy techniques. This finding is especially relevant if the goal is simply to provide estimates of physical activity, particularly for MVPA where the difference in daily estimate between no correction and multiple imputation was on the order of 1 minute/day. As the amount of bias in the estimate was of little practical significance, we focused on percent coverage as our criteria for best correction method in a regression setting, and recommend multiple imputation or random slope imputation, the latter of which is preferable in large data sets as it does not require minute level data.

Physical Activity in Cancer Survivors Undergoing Chemotherapy

A main theme of this dissertation was the methodological and computational issues that arise in physical activity measurement. However, it was also our goal to apply this theory to application and assess a new practice of physical activity measurement, namely long term continuous physical activity monitoring. In Chapter 3, titled *Continuous objective physical activity patterns during chemotherapy for breast cancer: The Activity in Treatment study*, we used commercially available Fitbit activity monitors to assess physical activity in 32 women throughout their chemotherapy for breast cancer, on a mean of 17 weeks. This allowed us to (1) fill a gap in the literature regarding the pattern of objectively measured physical activity throughout chemotherapy for breast cancer, (2) assess potential predictors of the trajectory of physical activity, and (3) assess the feasibility of having cancer survivors wear an activity tracker for an extended period. By using the Fitbit, which has been designed to be small, attractive, and acceptable for long term use, women were able to wear the device for the entirety of chemotherapy and achieve a high compliance (i.e., a mean of 84% of their chemotherapy days).

In the Activity in Treatment *(*ACT) study we observed a significant decline in both MVPA and total activity from the start of chemotherapy until approximately half way through chemotherapy. This equated to a 60 minute/week decrease in MVPA and an 8 hour/week decrease in total activity. Given the WHO recommendation of 150 min/week of MVPA,[14] this decrease of 60 min/week in MVPA implies that the previously observed activity levels below recommended levels following treatment[15-18] could likely stem from a decrease that occurs during treatment. Our observations are consistent with previous self-report research[19-21] including a large study (n=19,696) which assessed retrospective pre-diagnosis activity and activity at 6 months post-diagnosis and found a decrease in MVPA of around 2 hours/week for those who received chemotherapy.[19]

In addition to the trends in activity, we examined predictors of the rate of decline in activity. We found that cancer survivors with a HER2+ receptor status had significantly greater decline in MVPA. However, this result was not seen in the other study which examined receptor status as a predictor.[19] This difference may be because our study was restricted to those receiving chemotherapy and perhaps HER2 status predicts decline only among those receiving chemotherapy. We also found that increased age and BMI were associated with greater (although non-significant) decreases in MVPA, both of which are consistent with previous findings.[19,21,22]

Limitations

The research in this dissertation has several limitations. Chapters 1 and 2 were conducted in overweight, post-menopausal, breast cancer survivors who were also generally white and college educated.[23] This specific population makes methodological conclusions less generalizable. Specifically, in Chapter 1, the large disparity between self-report and 1952 cutpoints may not be seen in a younger, more fit, population as relative and absolute intensity may be more aligned. Nonetheless, understanding measurement differences for physical activity among older adults is of particular importance in breast cancer survivors, as breast cancer incidence is more than 7 times higher in women over fifty.[24] In Chapter 2 this specific population may have posed a limitation as it means the missing wear profile used to create the pseudo simulation could have been less representative of what we would see in breast cancer survivors overall. However previous research has found similar missingness patterns to the one used for our simulation.[25,26] The work in chapter 2 is also limited by the use of data from a 7-day, awake time, hip worn, wear protocol. This means that future research (Chapter 3 included) with 24-hour, wrist worn, wear protocols may experience different missingness patterns, especially when the devices are worn for extended periods of time (weeks or months). Future validations should be done using data generated from these different wear protocols to confirm.

Chapter 3 is limited by its small sample size because it was a pilot study. The ACT study was only able to achieve recruitment of 32 due to the small window of time between diagnosis and the initiation of chemotherapy. Nonetheless, because of the high daily wear compliance, we were still able to assess trends in activity throughout chemotherapy, although assessment of predictors of trend had limited power. The use of a commercially available Fitbit was a strength because it allowed us to capture long term physical activity trends with high wear compliance. However, the Fitbit provides the user feedback on steps and activity, which may have resulted in women being more active than they otherwise would have been. If women were more active as a result of the Fitbit, this would have attenuated our findings. However, a previous trial found that a Fitbit alone did not significantly increase physical activity beyond that seen in controls.[27] In addition, selection bias may have occurred by recruiting women into a study where they knew they would be provided a Fitbit. However, we attempted to identify and actively recruit all women who were eligible for the study, with an aim to reducing self-selection bias.

Future Directions

Previous research has highlighted physical activity as a key self-care tactic to increase health and well-being in breast cancer survivors.[28-33] The potential for a large amount of future research on this topic highlights how important it is for researchers to adopt standard practices for processing and analyzing activity data. At the same time, while self-report measurement of physical activity has generally given way to objective accelerometer measurement in research, these research grade accelerometers have laid the foundation for consumer based physical activity monitoring devices. The increased usability of commercially available devices allows for long term continuous measurement. Therefore, an important future direction is validating and standardizing these commercially available devices, especially over long-term wear periods.

Increased adoption of longer-term continuous monitoring makes it feasible to recruit participants prior to diagnosis to obtain a more complete picture of how physical activity changes over the course of diagnosis, treatment, and recovery from breast cancer. There has also been a call to incorporate continuous physical activity monitoring into oncology practice as a more accurate measure of functional status, thereby helping evaluate the suitability and effects of therapy in practice and in clinical research.[5] A recent study in breast cancer survivors showed support for technology-based exercise interventions and found that 90% reported an activity tracker would be the most helpful technology to incorporate.[34] Thus, increased validation and standardization of commercially available activity monitors can improve our ability to quantify physical activity and increase physical activity among breast cancer survivors.

Conclusions

Our results highlight the importance of targeting physical activity interventions during active treatment for breast cancer and lays the groundwork for incorporating long term continuous activity monitoring into this critical time. Given the benefit of physical activity in breast cancer survivors, both to increase health and as a potential clinical marker of functional status, future physical activity research in breast cancer survivors is likely to expand. This future work will likely include observational and interventional work with self-report and objective measures. Combined with the results of this dissertation, this expanding body of research emphasizes the importance of standardizing practices for processing and analyzing activity data.

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