# Association of self-directed walking with toxicity moderation during chemotherapy for the treatment of early breast cancer

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## Abstract

# Background

This study investigates associations of activity tracker steps with patient-reported toxicities during chemotherapy.

# Methods

Women with early breast cancer reported their symptom severity every 2–3 weeks throughout chemotherapy treatment and daily steps were documented through a Fitbit activity tracker. Relative risks (RR) and 95% confidence intervals (CI) were calculated using Poisson regression models with robust variance. For outcomes significant in unadjusted models, adjusted RRs were calculated controlling for race (dichotomized White and Non-White), age (10-year increments), and education level. Tracker step cut point (high step, low step) was determined by the mean. Cumulative incidence functions of moderate, severe and very severe (MSVS) symptoms were estimated using the Kaplan-Meier method and compared using a Cox proportional hazard model.

# Results

In a sample of 283 women, mean age was 56 and 76% were White. Mean tracker-documented steps/week were 29,625 (only 20% achieved the goal of 44,000 steps/week), with 55% walking below the mean (low step) and 45% above (high step). In multivariable analysis adjusted for age, race and education, high step patients had lower risk for fatigue [RR 0.83 (0.70,0.99)] ($p = .04$), anxiety [RR 0.59 (0.42,0.84)] ($p = .003$), nausea [RR 0.66 (0.46,0.96)] ($p = .03$), depression [RR 0.59 (0.37,0.03)] ($p = .02$), and ≥ 6 MSVS symptoms [RR 0.73 (0.54,1.00)] ($p = .05$). High step walkers also had 36% lower relative risk for dose reductions [RR 0.64, 95% CI 0.43,0.97)] ($p = .03$).

# Conclusion

Self-directed walking at a rate of at least 30,000 steps/week may moderate the severity of treatment side effects during chemotherapy for early breast cancer.

## INTRODUCTION

American Society of Clinical Oncology (ASCO) guidelines pertaining to exercise, diet and weight management during cancer treatment[1] endorse exercise to “reduce fatigue, preserve cardiorespiratory fitness, physical functioning and strength, and in some populations to improve QoL and reduce anxiety and depression”. This ASCO guideline is “strongly” recommended, but it is also noted in the guideline that the quality of supporting evidence is moderate to low. Numerous research questions remain regarding how and to what extent exercise is beneficial for adults with cancer, especially during active treatment[2].

Our study aimed to address two research questions. The first is whether exercise is associated with completion of the optimal chemotherapy regimen as planned[3,4]. Evidence from prior studies related to this question is mixed[5–8] and much of it pertains to the impact of pre-chemotherapy exercise history[7,9,10] and to a lesser extent to exercise

during chemotherapy[8,11–14]. A related question is whether clinician considerations that precipitate a decision to alter the treatment plan are amenable to modification through exercise.

Our second research question is whether exercise during active treatment can moderate the severity of common side effects of chemotherapy[15,16]. Which side effects are amendable to modification through exercise and to what extent are they modifiable? Also, the related question of "causality" – did engagement in exercise throughout chemotherapy lower symptom severity or did low symptom severity at baseline (pre-chemotherapy) enable engagement in higher levels of exercise during chemotherapy that, in turn, modified symptom severity?

This study utilizes data from single-arm intervention studies for which women with early breast cancer were enrolled in a home-based, self-directed walking program[15,17]. All participants were recruited prior to the start of their chemotherapy and were asked to wear a Fitbit activity tracker and self-report their symptom severity throughout treatment. The study first explores associations between activity tracker steps and regimen modifications (dose delay, dose reduction, early treatment discontinuation) and hospitalization. The study then explores associations between walking steps and symptom severity for 11 common chemotoxicities. And, in light of differing toxicity profiles among chemotherapy regimens in current clinical practice[15,16], we also compare the impact of walking under different chemotherapy regimens.

# METHODS

## Study Participants

This is a pooled analysis of data collected during three studies of women engaged in self-directed walking during chemotherapy for Stage I-III breast cancer. The studies were identical with the exception of age criteria at breast cancer diagnosis – women aged 21 to 64 years (NCT02167932), aged 65 or older (NCT02328313), and aged 21 or older (NCT03761706). We pooled the data in order to include all age groups in the current analysis and to increase sample size and power. The enrollment period was between 2014 and 2022. The studies were approved by the University of North Carolina at Chapel Hill (UNC) Lineberger Comprehensive Cancer Center (LCCC) Protocol Review Committee and the Institutional Review Boards (IRB) of participating sites. Women scheduled to receive chemotherapy with curative intent were approached and consented prior to chemotherapy initiation. Chemotherapy regimens were determined by treating oncologists in consultation with their patients depending on tumor stage and phenotype[18].

## Intervention

Consented patients in all three studies agreed to participate in a home-based walking intervention; there was no random or other assignment to various levels of exercise. Participants were encouraged to walk at least 150 minutes per week, at a place and pace they considered safe and sustainable throughout chemotherapy. They received a motivational booklet titled *Walk With Ease*[19] and were provided with an activity tracker that they were asked to wear during all waking hours. Study coordinators provided words of encouragement to walk when tracker data were uploaded during routine chemotherapy infusion visits. Further details regarding the intervention have been published previously[17].

In a prior analysis of participants in our walking studies[17], we reported that patients had great difficulty achieving the 150 minutes/week goal (an estimated 44,000 steps/week). Only 19% were fully adherent in our "real world"

intervention which entailed minimal exercise encouragement and no adherence supervision from research personnel. We also reported in our prior analysis that pre-chemotherapy (Baseline) history of vigorous physical activity, higher walking minutes/week, and greater outcome expectations from exercise were associated with the achievement of higher number of Fitbit steps/week. In turn, lower achievement of Fitbit steps/week was associated with non-White race, high school education or less, and never/almost never drinking alcohol. In multivariable analysis, race and walking minutes/week pre-chemotherapy remained independent predictors of steps/week during chemotherapy.

# Measures of Exercise

Activity tracker steps were uploaded into research computers by the Study Coordinator every 2 to 3 weeks depending on the patient's infusion schedule. For two studies (NCT02167932 and NCT02328313), the tracker was a Fitbit (Fitbit Inc., San Francisco CA) clip-on device. For the third study, the tracker was a Garmin Vivo (Garmin International Inc., Olathe KS) wristband device. Steps were tracked only during the chemotherapy portion of care; they were not tracked during anti-HER2 therapy that did not include a chemotherapy drug at the same time. In addition, participants were asked pre-chemotherapy about (1) self-reported walking minutes per week and (2) number of times per week they engaged in vigorous exercise.

# Patient-Reported Treatment Toxicities and Regimen Modifications

Every 2–3 weeks throughout their chemotherapy, patients were asked to rate symptom severity for 17 commonly observed side-effects from chemotherapy, with the response options of none, mild, moderate, severe or very severe (range 0 through 4). The symptoms were fatigue, insomnia, depression, anxiety, diarrhea, constipation, peripheral neuropathy, arthralgia, myalgia, pain (general), abdominal pain, nausea, vomiting, dyspnea, hot flashes, limb edema, and oral mucositis. For the current study, the focus is incidence and prevalence of symptoms – individual and total – rated moderate, severe or very severe (MSVS)[20]. Symptom reporting was conducted on-line (patient responses were entered directly into a REDCap database via tablet provided during the chemotherapy infusion) and utilized the validated Patient-Report Symptom Monitor (PRSM, first two studies)[21] (Appendix 1) or the PRO-CTCAE (Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events, most recent study)[22–24] when it became publicly available (Appendix 2), as described previously[15,25–27].

Data regarding regimen modifications and hospitalizations during chemotherapy were extracted from the participants' electronic medical record (EMR). In light of known toxicity variations among different drug regimens[15,16], events and MSVS symptom severity were analyzed for all participants combined and then separately for docetaxel versus paclitaxel/nab-paclitaxel regimens (most of which were sequential and included an anthracycline).

# Pre-Chemotherapy Assessments and Patient-Reported Outcome (PRO) Measures

Prior to chemotherapy initiation, study participants were assessed by study coordinators and completed several PRO measures on-line. Ranges (continuous variables) and cut points (for dichotomized variables) are presented in Table 1. Assessed measures included Timed Up and Go (TUG)[28] and Short Physical Performance Battery (SPPB)[29]. PROs included: Mental Health Index (MHI) to assess depression and/or anxiety[30], Instrumental

Activities of Daily Living (IADL)[31], Functional Assessment of Cancer Therapy-General (FACT-G) to assess wellbeing in four domains (physical, social/family, emotional, functional)[32], and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)[33].

Table 1
Study Participants (N = 283)

| Variables | Full Sample N = 283 | Tracker steps below the mean (low) N = 156 (55%) | Tracker steps above the mean (high) N = 127 (45%) | *p* value |
|---|---|---|---|---|
| **Activity tracker steps during chemotherapy** | | | | |
| Activity tracker steps during chemotherapy – per week | 29,625 (SD 18,118) (Range 2,107–97,920) | 16,361 (SD 7451.7) (Range 2,107 – 29,652) | 45,917 (SD 13,454) (Range 29,934 – 97,920) | **< .0001** |
| **Demographics at baseline (pre-chemotherapy)** | | | | |
| Age – mean (SD) | 56.5 (SD 12.2) (Range 24–83) | 58.9 (SD 12.8) (Range 24–82) | 53.5 (SD 10.8) (Range 31–83) | **< .0001** |
| Race | 214 (76%) | 107 (69%) | 107 (84%) | **.0005** |
| White | 52 (18%) | 41 (26%) | 11 (9%) | |
| Black | 17 (6%) | 8 (5%) | 9 (7%) | |
| Other | | | | |
| Education – | 35 (13%) | 30 (20%) | 5 (4%) | **.0002** |
| High school or less | 227 (87%) | 119 (80%) | 108 (96%) | |
| More than high school | | | | |
| Employed more than 32 hours/week | 165 (64%) | 104 (70%) | 61 (55%) | **.02** |
| No | 93 (36%) | 44 (30%) | 49 (45%) | |
| Yes | | | | |
| Married | 127 (45%) | 78 (50%) | 49 (39%) | .07 |
| No | 153 (55%) | 77 (50%) | 76 (61%) | |
| Yes | | | | |
| Living alone | 201 (79%) | 111 (76%) | 90 (83%) | .16 |
| No | 53 (21%) | 35 (24%) | 18 (17%) | |
| Yes | | | | |
| **Breast cancer diagnosis** | | | | |

| Variables | Full Sample N = 283 | Tracker steps below the mean (low) N = 156 (55%) | Tracker steps above the mean (high) N = 127 (45%) | *p* value |
|---|---|---|---|---|
| **Activity tracker steps during chemotherapy** | | | | |
| Breast cancer stage | 89 (31%) | 47 (30%) | 42 (33%) | .64 |
| 1 | 131 (46%) | 71 (46%) | 60 (47%) | |
| 2 | 63 (22%) | 38 (24%) | 25 (20%) | |
| 3 | | | | |
| Phenotype | 70 (25%) | 51 (33%) | 19 (15%) | **.0002** |
| HR-/HER2- | 34 (12%) | 24 (16%) | 10 (8%) | |
| HR-/HER2+ | 125 (44%) | 56 (36%) | 69 (54%) | |
| HR+/HER2- | 53 (19%) | 24 (16%) | 29 (23%) | |
| HR+/HER2+ | | | | |
| **Breast cancer treatment** | | | | |
| Chemotherapy Drug – taxane | 5 (2%) | 2 (1%) | 3 (2%) | .93 |
| None | 137 (49%) | 75 (49%) | 62 (49%) | |
| Paclitaxel/nab-paclitaxel | 135 (48%) | 75 (49%) | 60 (47%) | |
| Docetaxel | 4 (1%) | 2 (1%) | 2 (2%) | |
| Both | | | | |

| | | | | |
|---|---|---|---|---|
| **Chemotherapy regimen** | **81 (29%)** | **42 (27%)** | **39 (31%)** | **.31** |
| **Doxorubicin/cyclophosphamide before/after paclitaxel (AC-T or T-AC)** | **20 (7%)** | **14 (9%)** | **6 (5%)** | |
| **Doxorubicin/cyclophosphamide before/after paclitaxel/carboplatin** | **79 (28%)** | **39 (25%)** | **40 (32%)** | |
| **(AC-TC or TC-AC)** | **50 (18%)** | **32 (21%)** | **18 (14%)** | |
| **Docetaxel/cyclophosphamide (± anti-HER2) (TC)** | **51 (18%)** | **27 (18%)** | **24 (19%)** | |
| **Docetaxel/carboplatin/anti-HER2 (TCH)** | | | | |
| **Other** | | | | |
| **General health at baseline** | | | | |
| Self-reported walking minutes/week pre-chemotherapy | 139 (SD 165.25) (Range 0–1285) | 95.0 (SD 96.7) (Range 0–600) | 198.2 (SD 212.9) (Range 0-1285) | **< .0001** |
| Self-reported vigorous exercise pre-chemotherapy- | 122 (48.4) | 88 (62%) | 34 (31%) | **- < .0001** |
| Never, few times/month | 130 (52%) | 53 (38%) | 77 (69%) | |
| 1 or more times a week | | | | |
| Body Mass Index/BMI – mean (SD), range | 30 (SD 6.8) Range 16.8–64.9 | 31 (SD 7.2) (Range 17–65) | 27 (SD 5.7) (Range 26–43) | **< .0001** |
| Number of comorbidities – mean (SD), range | 0.99 (SD 1.2) (Range 0–6) | 1.3 (SD 1.2) (Range 0–5) | 0.6 (SD .97) (Range 0–6) | **< .0001** |
| **Assessments at baseline** | | | | |
| Timed Up and Go (TUG) | 178 (93%) | 103 (90%) | 75 (96%) | .16 |
| 12 seconds of less | 14 (7%) | 11 (10%) | 3 (4%) | |
| Greater than 12 seconds | | | | |
| Short Physical Performance Battery/SPPB – mean (SD); range 0 = worst to 12 = best performance | 10.6 (SD 1.8) (Range 3–12) | 10.1 (SD 2.0) (Range 3–12) | 11.3 (SD 1.2) (Range 6–12) | **< .0001** |

**Bold** print denotes statistical significanc

| | | | | |
|---|---|---|---|---|
| **Chemotherapy regimen** | **81 (29%)** | **42 (27%)** | **39 (31%)** | **.31** |
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| **Docetaxel/cyclophosphamide (± anti-HER2) (TC)** | **51 (18%)** | **27 (18%)** | **24 (19%)** | |
| **Docetaxel/carboplatin/anti-HER2 (TCH)** | | | | |
| **Other** | | | | |
| **Questionnaires at baseline** | | | | |
| Mental Health Index/MHI – range 0–43 (depressed score > = 12) | 187 (76%) | 98 (70%) | 89 (85%) | **.006** |
| Not depressed | | | | |
| Depressed | 59 (24%) | 43 (30%) | 16 (15%) | |
| Mental Health Index/MHI – range 0–20 (anxious score > = 6) | 147 (58%) | 75 (53%) | 72 (65%) | .06 |
| Not anxious | | | | |
| Anxious | 106 (42%) | 67 (47%) | 39 (35%) | |
| Instrumental Activities of Daily Living/IADL | 58 (21%) | 33 (22%) | 25 (20%) | .88 |
| <14 = limitations | | | | |
| 14 = no limitations | 222 (79%) | 122 (79%) | 100 (80%) | |

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| | | | | |
|---|---|---|---|---|
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| **Docetaxel/cyclophosphamide (± anti-HER2) (TC)** | **51 (18%)** | **27 (18%)** | **24 (19%)** | |
| **Docetaxel/carboplatin/anti-HER2 (TCH)** | | | | |
| **Other** | | | | |
| Functional Assessment of Cancer Therapy/FACT-General (higher score = higher wellbeing) – mean | 24.8 (SD 3.7) | 24.3 (SD 4.0) | 25.5 (SD 3.3) | **.008** |
| Physical wellbeing (range 0–28) | (Range 8–28) | (Range 8–28) | (Range 9–28) | .30 |
| Social/family wellbeing (range 0–28) | 24.7 (SD 4.6) | 24.4 (SD 5.0) | 25.0 (SD 4.2) | .53 |
| Emotional wellbeing (range 0–24) | (Range 2–28) | (Range 2–28) | (Range 6–28) | .08 |
| Functional wellbeing (range 0–28) | 19.2 (SD 3.6) | 19.3 (SD 3.8) | 19.2 (SD 3.4) | |
| | (Range 1–24) | (Range 1–24) | (Range 4–24) | |
| | 20.9 (SD 5.6) | 20.3 (SD 5.9) | 21.7 (SD 5.1) | |
| | (Range 0–28) | (Range 0–28) | (Range 6–28) | |
| Functional Assessment of Chronic Illness Therapy/FACIT-Fatigue Subscale (reverse scored so that higher score = less fatigue) (range 0–52) – higher score = less fatigue | 43.2 (SD 8.7) | 41.5 (SD 9.5) | 45.2 (SD 7.1) | **.0004** |
| | Range 5–52 | Range 5–52 | Range 18–52 | |
| Patient-reported symptoms prior to chemotherapy – rated moderate, severe or very severe (MSVS); mean | 1.5 (SD 2.1) | 1.6 (2.2) | 1.5 (SD 2.0) | .80 |
| | (Range 0–11) | (Range 0–11) | Range 0–11) | |

**Bold** print denotes statistical significanc

| | | | | |
|---|---|---|---|---|
| **Chemotherapy regimen** | **81 (29%)** | **42 (27%)** | **39 (31%)** | **.31** |
| **Doxorubicin/cyclophosphamide before/after paclitaxel (AC-T or T-AC)** | **20 (7%)** | **14 (9%)** | **6 (5%)** | |
| **Doxorubicin/cyclophosphamide before/after paclitaxel/carboplatin** | **79 (28%)** | **39 (25%)** | **40 (32%)** | |
| **(AC-TC or TC-AC)** | **50 (18%)** | **32 (21%)** | **18 (14%)** | |
| **Docetaxel/cyclophosphamide (± anti-HER2) (TC)** | **51 (18%)** | **27 (18%)** | **24 (19%)** | |
| **Docetaxel/carboplatin/anti-HER2 (TCH)** | | | | |
| **Other** | | | | |
| Patient-reported symptoms during chemotherapy – rated moderate, severe or very severe (MSVS); mean | 6.1 (SD 3.9) (Range 0–17) | 6.7 (SD 4.0) (Range 0–17) | 5.4 (SD 3.7) (Range 0–15) | **.002** |
| **Bold** print denotes statistical significanc | | | | |

[insert Table 1 here]

# Other Measures

Participants self-reported their age, race, education, employment, marital status, and living alone. Body Mass Index (BMI) and comorbidities were extracted from the EMR, as were breast cancer diagnosis and treatment.

# Statistical Considerations

Descriptive statistics were calculated for the study variables. Kruskal-Wallis Tests evaluated the association between continuous demographic and clinical characteristics with step count category, and Fisher's exact tests were used for categorical characteristics.

Relative risks (RR) and 95% confidence intervals (CI) were calculated using Poisson regression models with robust variance. RRs are reported for the entire sample, as well as subsets of patients based on chemotherapy regimen. For outcomes significant in the unadjusted models, adjusted RRs were calculated controlling for race (dichotomized as White and Non-White), age (in 10-year increments), and education level, as these variables were significantly associated with step count category in univariate analysis (Table 1).

Cumulative incidence functions of MSVS symptoms were estimated using the Kaplan-Meier method and compared using a Cox proportional hazard model. Adjusted analyses were calculated using a Cox model, controlling for race, age, and education. A two-tailed p of < .05 was considered significant. All analyses were performed with SAS statistical software (version 9.4; SAS, Cary, North Carolina).

## RESULTS

# Study Sample

The final sample included intervention study participants who had at least five weeks of activity tracker steps above 1000, the minimum that co-authors deemed necessary to indicate that the participant was wearing the activity tracker most of that week. These criteria resulted in the exclusion of 66 participants (19% of 349 enrolled in the three studies). The excluded group is slightly older and has a higher proportion of Black patients, but otherwise there were no significant differences between the included and excluded groups with regard to chemotherapy regimens (Appendix 3).

# Activity Tracker Steps During Chemotherapy

Only 20% achieved the goal of 44,000 steps/week and was considered too small a sample for dichotomization at that cut point. Average tracker steps for the full sample were 29,625 steps/week, with 55% below this mean (low step) and 45% above (high step) (Table 1). This dichotomized variable – high step vs low step – is the primary measure of exercise for all subsequent analyses. Low step participants had weekly steps ranging from 2,107 to 29,652 and high step from 29,934 to 97,920 ($p < .0001$).

# Sample Characteristics

Table 1 presents a descriptive overview of the final sample of 283 patients. Mean age at study enrollment was 56 (range 24–83), 18% were Black and 6% other than White or Black, 87% had more than a high school education, 64% were employed less than 32 hours/week, and 79% were not living alone. Low step participants were on average older, Black, high school education or less, and employed less than 32 hours/week.

Low step participants included a higher proportion with hormone receptor-negative tumors ($p = .0002$). There were no significant differences in chemotherapy regimens between the two groups ($p = .31$). For the entire sample, chemotherapy regimens were: 29% doxorubicin/cyclophosphamide before/after paclitaxel (AC-T or T-AC), 7% doxorubicin/cyclophosphamide before/after paclitaxel/carboplatin (AC-TC or TC-AC), 28% docetaxel/cyclophosphamide (± anti-HER2) (TC), 18% docetaxel/carboplatin/anti-HER2 (TCH), and 18% other.

Low step participants had baseline (pre-chemotherapy) fewer self-reported walking minutes/week, were less likely to have engaged in vigorous exercise, had higher body mass index/BMI, and higher number of comorbidities. Low step participants included a higher proportion rated depressed and scoring slightly worse on the SPPB test, FACT-G physical wellbeing, and FACIT-Fatigue.

At baseline (pre-chemotherapy), the average number of symptoms rated moderate, severe or very severe (MSVS) was 1.5 (Range 0–11) with no significant difference between high and low step groups. During chemotherapy, low step participants averaged 6.7 MSVS symptoms (Range 0–17) compared to 5.4 symptoms (Range 0–15) for high step participants ($p < .0001$). In Fig. 1, the percentage reporting MSVS severity is shown for 17 symptoms pre-chemotherapy as compared to during chemotherapy for the full sample.

[insert Fig. 1 here]

# Regimen Modifications and Associations with Activity Tracker Steps

One or more dose delays during chemotherapy infusion were experienced by 16% of study subjects (N = 44), 35% had at least one dose reduction (N = 98), 12% had early treatment discontinuation (N = 34), and 14% were hospitalized (N = 38) during their chemotherapy (Appendix 4). In multivariable (MV) analysis adjusted for race,

age and education (significant in univariate analysis of associations with tracker steps), high step participants had 36% lower risk for dose reduction [RR 0.64 (95% CI 0.43,0.97)] ($p = .03$). There were no other significant differences between high and low step participants for dose delay ($p = .64$), early treatment discontinuation ($p = .54$), or hospitalization ($p = .94$).

Primary reasons for regimen modifications, as recorded in clinician notes, are listed in Appendix 4. Neuropathy is noted for 17% of dose delays, 36% of dose reductions, and 27% of early treatment discontinuations. Fatigue is the cited reason for 6% of dose reductions and 9% of early treatment discontinuations. Nausea and/or vomiting accounted for 5% of dose reductions. Otherwise, reasons listed by clinicians pertained primarily to hematological and other clinical factors such as neutropenia, anemia, thrombocytopenia, neutropenic fever, and port complications.

# Symptom Severity and Associations with Activity Tracker Steps

In Table 2, we present univariate associations between activity tracker steps and risk for moderate, severe or very severe scores (as compared to none or mild) for 11 symptoms with the highest proportion rated MSVS (see Fig. 1) and mean number of toxicities ≥ 6 rated MSVS. The associations are presented as Relative Risk (RR with 95% Confidence Interval) for participants with high steps (low steps is the Referent).

Table 2
Univariate associations of “high step” walking with individual symptoms rated moderate, severe or very severe (MSVS) during chemotherapy – relative risk (RR) with 95% confidence interval

| Chemotherapy | Fatigue | Insomnia | Arthralgia | Anxiety | Constipation | Myalgia |
|---|---|---|---|---|---|---|
| All participants | **0.85 (0.73,0.98)*** | 0.89 (0.73,1.08) | 0.76 (0.56,1.03) | **0.64 (0.47,0.87)**** | 0.75 (0.53,1.04) | 0.76 (0.56,1.03) |
| Taxane | 0.92 (0.78,1.09) | 0.89 (0.68,1.16) | 0.82 (0.56,1.20 | 0.76 (0.50,1.15) | 0.92 (0.62,1.36) | 0.82 (0.56,1.20) |
| Paclitaxel/nab-paclitaxel | **0.71 (0.54,0.94)*** | 0.80 (0.59,1.09) | **0.58 (0.34,1.00)*** | **0.46 (0.28,0.77)**** | **0.50 (0.26,0.96)*** | 0.65 (0.38,1.09) |
| Docetaxel | | | | | | |
| **Chemotherapy** | **Pain (general)** | **Nausea** | **Hot flashes** | **Peripheral neuropathy** | **Depression** | **Mean number of toxicities ≥ 6 rated MSVS** |
| All participants | 1.09 (0.83,1.44) | **0.71 (0.51,0.99)*** | 1.16 (0.86,1.57) | **0.65 (0.47,0.91)*** | **0.65 (0.44,00.95)*** | **0.67 (0.51,0.88)**** |
| Taxane | 0.97 (0.67,1.40) | 0.78 (0.53,1.16) | 0.98 (0.66,1.46) | 0.71 (0.48,1.05) | 0.81 (0.49,1.32) | **0.67 (0.48,0.93)*** |
| Paclitaxel/nab-paclitaxel | 1.25 (0.82,1.91) | **0.53 (0.29,0.98)*** | 1.31 (0.80,2.14) | **0.52 (0.27,1.00)*** | **0.47 (0.22,0.85)*** | **0.55 (0.33,0.91)*** |
| Docetaxel | | | | | | |
| **Bold** print denotes statistical significance. *p ≤ .05, **p ≤ 01, ***p ≤ .001 – indicated in bold type. | | | | | | |
| Referent is “low step” walking. | | | | | | |
| Paclitaxel/nab-paclitaxel regimens generally included anthracycline. | | | | | | |

[insert Table 2 here]

In univariate analysis, high steps were associated with lower risk for MSVS fatigue, anxiety, nausea, peripheral neuropathy, depression, and ≥ 6 of symptoms. In MV analysis, all associations between high steps and toxicities remained significant, except peripheral neuropathy: fatigue [RR 0.83 (0.70,0.99)] ($p$ = .04), anxiety [RR 0.59 (0.42,0.84)] ($p$ = .003), nausea [RR 0.66 (0.46,0.96)] ($p$ = .03), depression [RR 0.59 (0.37,0.03)] ($p$ = .02), and ≥ 6 MSVS symptoms [RR 0.73 (0.54,1.00)] ($p$ = .05).

# Cumulative Symptom Incidence by Tracker Steps Category

Figure 2 presents cumulative incidence curves for MSVS severity for four symptoms over 150 days (presented in 30-day increments), comparing study subjects who walked above average (high step) with those who walked below average (low step). In MV analysis adjusted for race, age and education, high step participants had significantly lower fatigue (p = .006), anxiety (p = .008), depression (p = .04), and nausea (not shown in Fig. 2, p = .023). There was no significant difference in MSVS CIPN (p = .08).

[insert Fig. 2 here]

In univariate analysis (Table 1), high step subjects had significantly lower FACIT-F Fatigue score, indicating less fatigue at baseline, and lower frequency of MHI depression. To reduce the effect of baseline symptoms on cumulative incidence, we ran hazard models for MSVS fatigue and depression *excluding* patients who reported MSVS fatigue or depression at baseline, respectively, as a sensitivity analysis. In these revised models (Fig. 3), high step participants continued to have significantly lower fatigue (p = .02) and lower depression (.03).

[insert Fig. 3 here]

# DISCUSSION

The objective of this study was to explore associations of self-directed walking with relative risk for regimen modifications and moderate, severe or very severe (MSVS) symptom severity during commonly-used chemotherapy regimens with differing toxicity profiles[15,16]. All study participants were encouraged to walk at least 150 minutes/week, which equals about 44,000 steps per week[17]. Actual tracker steps achieved by our study participants were far below this goal, but our data offered a wide range of engagement in walking, thereby allowing for meaningful two-group comparisons between participants who walked above (high step) versus below the mean (low step) of approximately 30,000 steps/week.

We observed demographic, exercise history, BMI, comorbidity and baseline fatigue differences between the two walking groups, reflecting factors associated with higher versus lower levels of walking steps during chemotherapy for early breast cancer that we have reported in previously analyses[17]. Other studies have similarly noted lower exercise compliance among patients with obesity as compared to those with no obesity[34]. Importantly, in the current study, there were no significant differences between the two steps groups in proportions receiving the four most common chemotherapy regimens, thereby eliminating potentially crucial confounders to our comparison of high vs low step walkers under differing treatment scenarios.

In our analysis of associations between trackers steps and regimen modifications during chemotherapy, a significant association was observed only for dose reductions, where there was a 36% lower risk among high step

participants. Among the reasons listed in clinician notes for regimen changes, the most commonly noted reasons were hematological and other clinical toxicities, which are not likely to be modifiable through moderate exercise. Prior studies have shown that peripheral neuropathy may be modifiable through exercise at the start of chemotherapy[35], but we did not observe this benefit in our sample. It is possible that higher intensity exercise is required. It is well-established that exercise is effective in managing fatigue during chemotherapy and beyond[36], and out study provides further corroboration. In multivariable analysis adjusted for age, race and education, high step patients also had lower risk for anxiety, nausea, depression, and ≥ 6 MSVS symptoms.

The cumulative incidence plots shed some light on causality. Study subjects were mostly at the same severity level for all symptoms at Week 0, with the exception of fatigue and depression. When we limited our analysis to participants who were not already reporting high levels of fatigue and depression prior to chemotherapy, we continued to observe significant benefits from walking in high versus low step participants. With roughly the same levels of fatigue at Week 0, high step walkers had significantly lower fatigue over the duration of their chemotherapy, and similarly significantly less depression.

Our study has some limitations. Adherence to exercise interventions during chemotherapy treatment can be challenging[17,37] and most patients in our sample did not achieve the goal of 150 min/week of walking. This deserves further exploration through a more supervised exercise intervention to help improve adherence rates. Further, the generalizability of our findings is limited to the extent our study subjects agreed to participate in an exercise intervention study and include a high proportion of women with more than a high school education, both of which are not necessarily representative of the general population of women with early breast cancer. A randomized controlled trial design of our home-based, self-directed walking intervention may produce contradictory results or further strengthen our findings.

The strengths of our study include objective activity tracker data to measure exercise and prospective patient-generated symptom reports throughout chemotherapy for a wide range of symptoms. Our dichotomization of walking steps as above-vs-below the mean – rather than adherence-vs-non-adherence to walking step targets – provided a valid and productive method for evaluating the impact of self-directed walking on regimen modifications and treatment toxicities. And our prospective data on symptom severity over 150 days – showing a common starting point – provides insights into the causality, albeit not conclusive.

Our findings suggest that self-directed walking may moderate the severity of common side effects of chemotherapy and contribute to the literature documenting to the benefits of exercise for women diagnosed with early breast cancer[38]. Regardless of symptom severity at Week 0, many patients can experience the benefits of symptom modification even when they do not achieve guideline-recommended levels of activity.

# Declarations

**Lay Summary**:

- This study explores whether home-based, self-directed walking throughout chemotherapy for early breast cancer can moderate the severity of treatment-related side effects (symptoms).
- Study participants who whose tracker steps were above the mean for the full sample (high step) reported fewer instances of moderate, severe or very severe symptoms for 11 commonly reported chemotherapy

toxicities as compared to participants who walked below the mean (low step).

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**Author Contributions**: **Kirsten A. Nyrop**, **Annie Page**, **Allison M. Deal**, and **Hyman B. Muss:** Conceptualization, data curation, formal analysis, funding acquisition,investigation, methodology, project administration, resources,software, supervision, validation, visualization, writing–original draft, and writing–review and editing. **Chad Wagoner, Erin EA Kelly, Gretchen G. Kimmick**, **Anureet Copeland, JoEllen C. Speca, and William A Wood:** Writing–review and editing. All authors reviewed the manuscript.

### Declarations

Ethics approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Institutional Review Boards of the University of North Carolina at Chapel Hill and Duke University.

**Competing Interests**: The authors declare no competing interests.

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# Figures

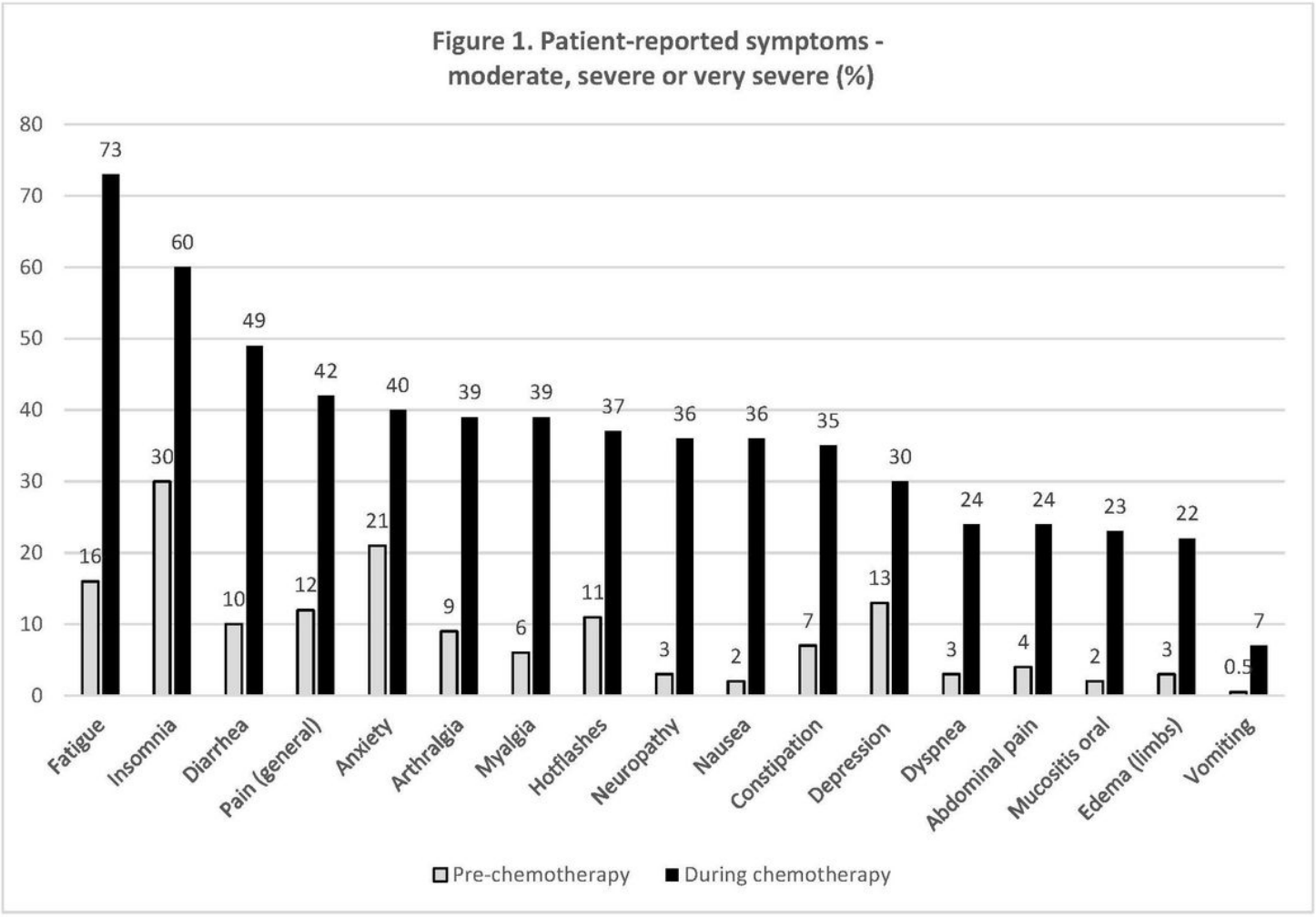
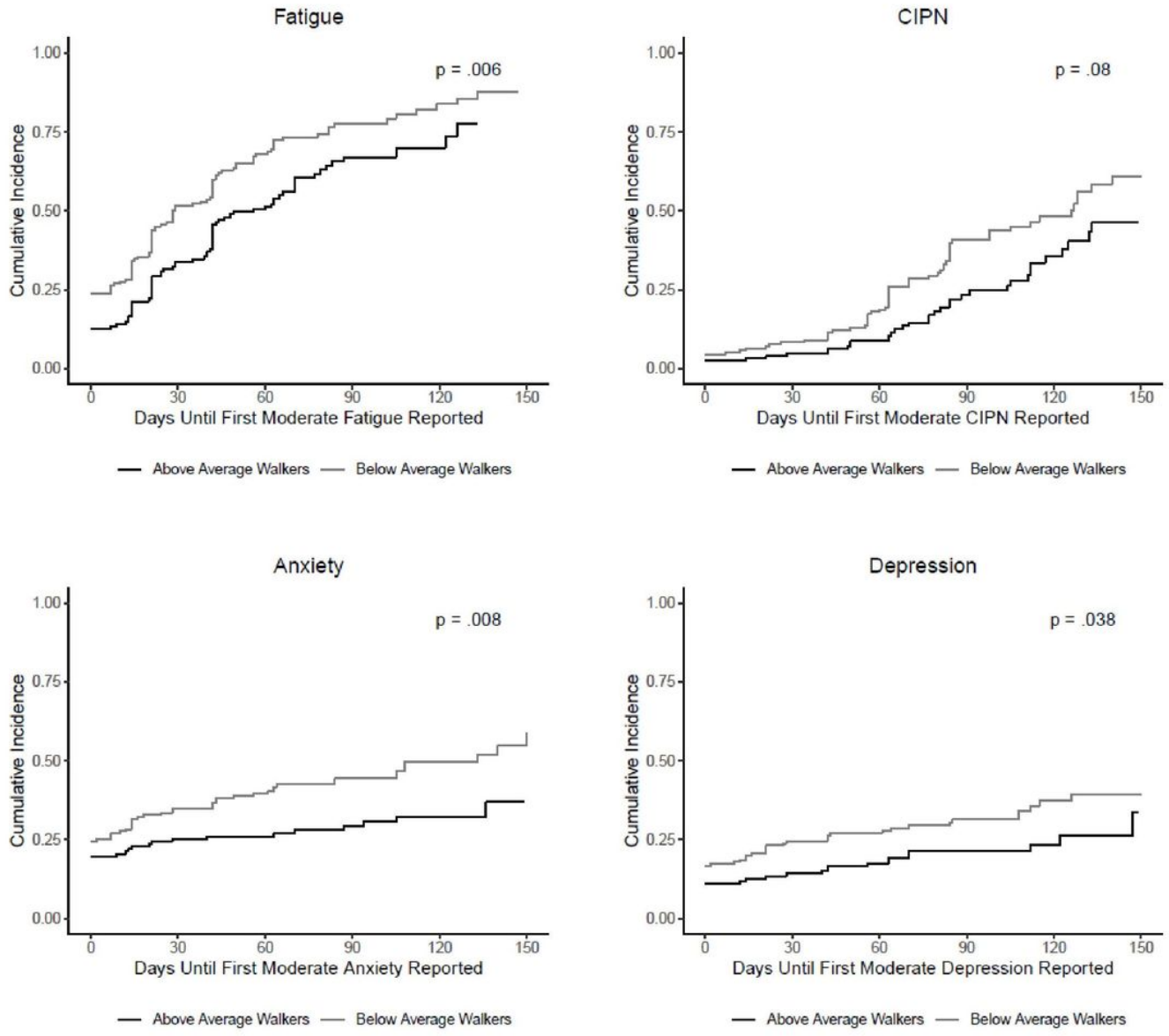



**Figure 1**

See image above for figure legend.




## Figure 2

Cumulative Incidence Curves (p value adjusted for race, age and education)

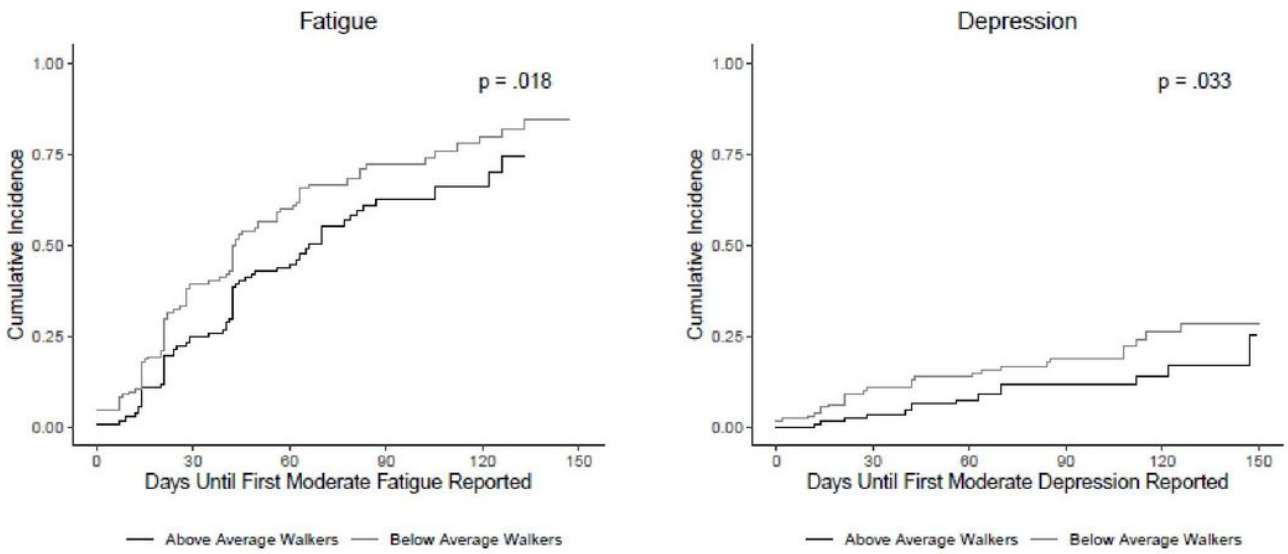



**Figure 3**

Cumulative Incidence Curves of subjects who did not report moderate, severe or very severe fatigue or depression prior to chemotherapy initiation (p values adjusted for race, age and education)

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Appendix1PRSM.pdf
- Appendix2PROCTCAE.pdf
- Appendix3includedvsexcludedFinal.docx
- Appendix4REASONSforadverseeventsFinal.docx