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Health-related quality of life factors associated with completion of a study delivering lifestyle exercise intervention for endometrial cancer survivors

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1. Background

It is estimated that 54,870 women will be diagnosed with endometrial cancer in the United States in 2015 [1]. Among those diagnosed, 10,170 women are predicted to die of the disease. Over the course of lifetime, the estimated risk of developing endometrial cancer is 2.8%, with median age at diagnosis of 62 years. Literature suggests that obesity is one of the most significant risk factors for endometrial cancer [2–4], and continues to be a long-term threat to health and quality of life survivors [5–8].

In order to improve quality of life and reduce obesity-related comorbidities of endometrial cancer patients, there has been an increased interest in delivering lifestyle interventions to this population [9–10]. However, behavioral interventions targeted at changing patterns of sedentary and physical activities in cancer survivors have often shown to have low adherence [6,11]. Existing literature suggests associations between physical activity and quality of life [12–13], but limited data exist on whether baseline quality of life is associated with completion of exercise intervention studies in cancer survivors.

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Conflict of Interest

None of the authors have any relevant financial interests or conflicts to disclose.

COMPLIANCE WITH ETHICAL STANDARDS

Ethical Approval

Project Steps to Health procedures and materials have been reviewed and approved by the Institutional Review Boards of the University of Texas MD Anderson Cancer Center.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

The aim of this study is to explore linear- and non-linear associations between various domains of quality of life and study completion in a sample of endometrial cancer survivors. We hypothesized that (1) participants' reporting higher quality of life would be more likely to be study completers, and that (2) associations between important quality of life factors and odds of study completion would be non-linear.

2. Methods

2.1. Sample

This study is a secondary data analysis of the Steps to Health project, which was a one-arm longitudinal study designed to investigate factors influencing exercise adoption in endometrial cancer survivors receiving an exercise intervention. Participants were recruited from M.D. Anderson Cancer Center's Gynecologic Oncology Center and the Gynecologic Oncology outreach program, as well as the Gynecological Oncology of Houston, a Houston-based community practice (study conducted from January 2007 to December 2009). Potentially eligible participants were identified using medical records data, and were approached through telephone, mail, or during the clinic appointment. Inclusion criteria were: 1) endometrial cancer survivors diagnosed with Stage I, II, or IIIa in the last five years who finished surgery or radiation treatment for at least six months; 2) able to speak and read English; 3) oriented to person, time, and place such as one's ability to simply identify their name, where they currently are, and day of the week; and 4) who had physician approval to engage in moderate physical activity. Interested participants were excluded from the study if they had met physical activity guidelines for at least 6 months which was defined as doing moderate-to-vigorous intensity exercise 5 days per week for at least 30 minutes or doing vigorous intensity exercise 3 days per week for at least 20 minutes. Survivors participated in a 6-month longitudinal study with assessment periods: baseline (T0), 2 months (T1), 4 months (T2), and 6 months (T3). All assessment periods had laboratory and home-based components. Laboratory assessments included cardiorespiratory fitness test and questionnaires. Home-based components used ecological momentary assessment (EMA) to capture participants' behavior or state and real time and accelerometers to measure physical activity in real living conditions. Previous publications from this study reported associations between participants' self-efficacy and exercise behavior [14] and differences between obese and non-obese participants in their response to the exercise intervention [16]. Further details on the study design have published previously [14–16].

2.2. Intervention

The intervention included: a personalized exercise prescription given at the baseline assessment based on cardiorespiratory fitness, 14 telephone counseling sessions, printed support materials, and a pedometer. The exercise recommendation was prepared by a masters-level exercise physiologist to provide at least 30 minutes of moderate-intensity exercise per day, for at least five days per week. The telephone counseling sessions consisted of 20- to 30-minute calls designed to increase adherence by providing feedback on participant exercise progress, discussing health issues that may interfere with exercise, and suggesting behavioral skills to overcome such barriers. The calls were scheduled weekly in months 1 and 2, bi-weekly in months 3 and 4, and monthly in months 5 and 6. Printed

support materials describing the behavioral techniques were mailed to participants prior to telephone counseling. Pedometers were provided to help participants track their levels of exercise.

2.3. Measures

Quality of Life—Quality of life was measured using five different questionnaires self-administered at the T0 and T3 assessments.

SF-36: The Medical Outcomes Study (SF-36) US Standard Version 1.0 is a 36-item survey that measures physical and mental health. The questionnaire consists of 8 scales (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health). The possible answers to the questions are either dichotomous “yes-no” or Likert scaled responses of varied length. For each of the 8 subscales, percentage score is calculated to represent score range from 0 (lowest level of functioning) to 100 (highest level of functioning). The SF-36 Version 1.0 was found to have high internal consistency reliability coefficients above .80 (the accepted standard) in all scales except Social Functioning which had a median coefficient of .76 [17]. Internal consistency (Cronbach’s alpha) in this sample was high for the subscales (α .80) except for mental health (α =.77), and general health (α =.77).

QLACS: The Quality of Life in Adult Cancer Survivors (QLACS) is a 47-item survey which has 28 cancer-specific items and 19 generic items [18]. Five cancer-specific domains (appearance concerns, financial problems, distress over recurrence, family-related distress, and benefits of cancer) and 7 generic domains (negative feelings, positive feelings, cognitive problems, sexual problems, physical pain, fatigue, and social avoidance) are identified. The responses used a scale from 1 (Never) to 7 (Always). Initial psychometric evaluations indicate that the Cronbach’s alphas were greater than 0.8 with a range from 0.81 to 0.88 for the cancer-specific domains [18], and above 0.7 with a range of 0.72 to 0.91 for generic domains [18]. Internal consistency (Cronbach’s alpha) in this sample was high for the subscales (.80) in this sample except negative feelings (α =.74), and appearance concerns (α =.56).

Perceived Stress Scale (PSS): The Perceived Stress Scale (PSS) is a 14-item questionnaire that measures the participant’s perceived stress in addition to their view of their lives [19–20]. The survey uses Likert rating scales with questions that measure the frequency of experiences during the last 4 weeks from “Never” (0) to “Very Often” (4). The PSS had high Cronbach alphas ranging 0.84 to 0.86 across the three samples tested during the initial development of the instrument [19]. A perceived stress score is derived as sum of the responses. Internal consistency (Cronbach’s alpha) in this sample was high (α =.86).

Pittsburgh Sleep Quality Index (PSQI): The Pittsburgh Sleep Quality Index (PSQI) is a 19-item survey that measures the quality and patterns of sleep in the last 4 weeks [21]. The responses are on a “Not during the past month (0)” or “Very good (0)” to “Three of more times a week (3)” or “Very Bad (3)” Likert-ranking scale where a higher score indicates poorer sleep. The PSQI results in seven components scores that are calculated into

a global score where a score greater than 5 reflects a person with poor sleep. The instrument reports a Cronbach's alpha of 0.83 across the seven components [21]. Internal consistency (Cronbach's alpha) in this sample was $\alpha=.71$.

Brief Symptom Inventory 18 (BSI-18): The Brief Symptom Inventory 18 (BSI-18) is an 18-item survey that identifies psychological distress and psychiatric disorders with 6-items on each of the following specific criteria: somatization, depression, and anxiety [22]. The three criteria are summed to comprise the Global Severity Index (GSI). The responses are on a 0 to 4 Likert Scale where 0 represents "Not at all" and 4 represents "Extremely". Across the four criteria, the internal consistency reliability coefficient was at least 0.74 (Somatization) with a maximum of 0.89 (GSI). Internal consistency (Cronbach's alpha) for the GSI in this sample was high ($\alpha=.84$).

Study completion—Participants who have completed *any* of the the laboratory (cardiorespiratory fitness test or questionnaires) or the home-based components (EMA or accelerometer) for *all* scheduled assessment times (T0, T1, T2, T3) were considered as completers. Otherwise, they were considered to be non-completers. For example, if an individual missed all laboratory and home-based components at any of the scheduled assessment times, then the individual is classified as a non-completer. On the contrary, if an individual completed any of the laboratory or home-based component for all assessment times, then the person was considered a completer.

2.4. Statistical Methods

Sample characteristics between study completers and non-completers were compared using Fisher's exact and Welch's two sample t-tests. Associations between baseline quality of life factors and study completion were examined using generalized additive models [23]. Generalized additive models (GAMs) are an extension of the generalized linear models that accommodates response variables with distributions other than the normal distribution (i.e. counts or binary outcomes), as well as non-linear associations between the predictors (e.g., quality of life subscale) and the response function (e.g. log odds of study completion). In GAMs, the effects of predictor variables are estimated by fitting a smoothing curve through the data. The estimated effect of the predictor from GAM can either be linear or non-linear, depending on the nature of association. This approach is particularly attractive when there is no a priori reason for choosing a particular response function (i.e. linear, quadratic, cubic, log, square root, etc.). A logit link function was used to associate log odds of study completion to the covariates.

In order to avoid fitting large number GAMs for each of the quality of life factors measured with instruments: SF-36, QLACS, PSS, PQSI, and BSI-18, we performed a variable and function selection procedure [24–25]. The objective of this variable selection procedure was to identify a handful of quality of life factors highly associated with the odds of study completion among: i) 8 subscales and 2 composite scores (Physical and Mental Component Scores) from SF-36, ii) 12 subdomains and 2 total scores (for cancer specific and generic) from QLACS, iii) 3 symptom specific and 1 total score from BSI-18, and iv) two global scores from each of PSS and PQSI. Our variable selection procedure

considered all 30- quality of life factors described above, both in linear and in non-linear form. This helped us to simultaneously evaluate important quality of life factors associated with study completion, and also examine whether the association can be best explained in linear or non-linear fashion. Specifically, the variable selection procedure was carried out by introducing a binary latent variable for each of the coefficients of a saturated model including all potential predictors specified in both linear and non-linear fashion [24–25]. The binary (1 or 0) indicator variable represented a decision whether to include or exclude the variable (either in linear or non-linear associations to the outcome). A measure of variable importance was quantified as a probability of the indicator being 1, generated using a Markov chain Monte Carlo (MCMC) inference. The variable selection algorithm was implemented using an R package *spikeSlabGAM* [24], by generating the posterior distribution of the inclusion probability. The MCMC inference was based on 60,000 samples from 3 Markov chains, each running after a burn-in sample of 10,000. We selected quality of life factors with highest posterior inclusion probability (with minimum value of marginal inclusion probability specified as .25, as suggested by [24]).

Final models presented in this study fitted GAMs for each quality of life factors identified by the variable selection procedure, in associations to the log odds of study completion, adjusting for important covariates. If non-linear associations between the quality of life factor and the outcome variable were identified in the variable selection procedure, cubic splines (to allow for wide range of possible shapes) were used to estimate the smoothing curves in the GAMs. Optimal smoothing parameters were chosen using the generalized cross validation procedure [26], with the maximum number of knots restricted to 4, following the widely adopted suggestion by Keele [27]. In order to control for the type I error in testing multiple hypotheses for associations between quality of life factors and odds of study completion, p-values were adjusted for false discovery rate [28]. In this method, adjusted values are simply obtained by ordering the p-values from smallest to largest and multiplying it by N/rank , where N is the number of tests. If the adjusted p-value is larger than the largest p-value, then it is substituted with the largest p-value. All statistical analyses were performed using R version 3.2.0 [29]. The GAMs were fitted using the *mgcv* package [30]. Statistical significance level was set at 0.05 for all tests.

3. Results

3.1. Descriptive Statistics

A flow diagram illustrates cancer survivors who were potentially eligible, approached, and enrolled to the study (Figure 1). The majority of the participants were non-Hispanic whites (75%), had at least some college education or received a two-year degree (77%), and obese (64%). On average, participants were aged 57 years (Range: 25–76), had Body mass index (BMI, kg/m^2) of 34 (Range: 19–69), and 2.2 years (Range: .5–5.2) from time of diagnosis of endometrial cancer.

All participants in the Steps to Health study completed at least one of the laboratory or home-based component at baseline. On month 2, 13 individuals missed all laboratory and home-based components. Subsequently, only 83 and 79 participants completed at least one of the laboratory or home-based components, respectively, at months 4 and 6. Overall,

74 participants were classified as completing the study, since they completed at least one component from laboratory or home-based assessment for all measurement periods. The remaining 26 percent of the participants missed all scheduled assessments, for at least one measurement time. Participant characteristics of race and disease stage differed between completers and non-completers in Fisher's exact tests (Table 1): the completer group had higher proportions of non-Hispanic whites, and survivors diagnosed with disease stages II or higher. Among non-completers, participant who completed no measurement components beyond baseline were younger in age compared to those who completed at least one during months 2, 4, and 6 ($p=.004$), while no statistically significant differences were found between characteristics of race, education, disease stage, and treatment.

3.2. Associations between study completion and quality of life

Generalized additive models were used to explore associations between study completion and quality of life, adjusting for individuals' race (dichotomized as non-Hispanic whites vs. other), and disease stage (dichotomized as disease stage I vs. higher), which significantly differed between completers and non-completers.

Important quality of life factors associated with the odds of study completion were identified using a variable selection procedure described in the statistical methods section. A total of thirty quality of life factors from five different questionnaires were considered. The variable and function selection algorithm suggested considering non-linear associations between subscales of bodily pain (SF-36) and anxiety (BSI-18), and the odds of study completion. Therefore, we fitted two GAMs, each considering bodily pain (SF-36) and anxiety (BSI-18) scores as main predictors, adjusting for individuals' race (dichotomized as non-Hispanic whites vs. other) and disease stage (dichotomized as disease stage I vs. higher). Both quality of life factors, bodily pain ($p=.025$) and anxiety ($p=.035$) were significantly associated with the odds of study completion (p-values were adjusted for false discovery rate as described in the statistical methods section). The non-linear associations between the quality of life factors and the odds of study completion were interpreted visually. The estimated smoothing curve for the bodily pain score (Figure 2) indicate that improvements in the bodily pain quality of life were associated with increased odds of study completion, especially for individuals in lower range (i.e. 10–45), when the model was adjusted for covariates of race and disease stage. An improvement in the bodily pain quality of life did not seem to contribute to the increase in the odds of study completion for individuals with relatively higher score (i.e. 45–100). Associations between the odds of study completion and anxiety score (BSI-18) showed two different trends (Figure 3): whereas increases in anxiety was associated with higher odds of completion for individuals with low (i.e. anxiety score 0–4) anxiety levels, increase in anxiety contributed to lower odds of study completion for individuals with anxiety scores of approximately 5 to 10. Although individuals with high anxiety levels (i.e. anxiety score 10–17) showed a similar trend as individuals with low anxiety (i.e. anxiety score 0–4), there were greater degree of uncertainty in this score range, since only a small fraction of individuals had anxiety scores higher than 10. The model was adjusted for covariates of race and disease stage.

4. Conclusions

4.1. Summary of Findings

In summary, results from this study indicate that quality of life domains of pain and anxiety may be important factors associated with study completion in exercise intervention studies for endometrial cancer survivors. Quality of life domains of bodily pain contributed in a non-linear way, suggesting that improvements in this factor may be associated with participants' study completion, especially for individuals under greater impairments. Lastly, increased levels of anxiety were associated with lower odds of study completion for individuals with BSI subscale score between 5–10, but associated with higher odds of study completion for individuals for very low anxiety (BSI-18 subscale score between 0–4).

4.2. Implications

Participants' study completion can be challenging in studies delivering lifestyle exercise interventions to cancer survivors. Endometrial cancer survivors have a high BMI compared to all other cancer types [31], and the comorbidities associated with obesity generally have a negative impact on quality of life outcomes [32–33].

While several studies have reported differences in the quality of life between study completers and non-completers in exercise studies of non-cancer patients [34–35], these results may not be generalizable to cancer survivors. For example, in the Program for All-Inclusive Care of Elders (PACE), a study aimed at increasing moderate exercise among functional impaired older African American women [34], non-completers were more likely to report higher scores on scales related to depression than completers. In another investigation of non-cancer patients called the Look AHEAD (Action for Health in Diabetes) study [35], subjects who missed visits had lower functioning scores in the SF-36 domains of general health, role emotional, and mental health than completers in this study. Interestingly, none of these quality of life factors have been identified as important attributes relating to study completion in our investigation of endometrial cancer survivors. This suggests that endometrial cancer survivors may have different domains of quality of life factors associated with study completion.

Several existing literature have suggested non-linear relations between different health-related quality of life factors [36], between health-related quality of life factors and response to environmental stress [37], or between quality of life factors and disease status [38]. However, non-linear associations between quality of life factors and odds of study completion have rarely been investigated. To our knowledge, this is a first study to examine non-linear associations between quality of life factors and study completion, in a sample of endometrial cancer survivors. We have implemented an exhaustive exploration of a total of 30 quality of life factors from five instruments to determine linear and non-linear associations to the odds of study completion through a MCMC inference.

Findings from our study fill the gap in the literature on health-related quality of life factors contributing to completion of study delivering lifestyle exercise intervention for endometrial cancer survivors. Results suggest that study completion may be improved if participants with more disruptions in quality of life from pain and anxiety were identified at the beginning of

the study. While our findings for pain may simply suggest a threshold where improvements in the pain related quality of life no longer affects the odds of staying in the study, the relation between anxiety and study completion is more intriguing. Such inverse-U shaped curve has often been proposed to study optimum levels of stress and arousal for effective learning [39] and sports performance [40]. The theory that performance of a certain task may be impaired under conditions above or below the optimal arousal or stress levels may be relevant in explaining the inverse-U shaped curve we have found in explaining the associations between anxiety and the odds of study completion.

In summary, conclusions from this study suggest that study completion rates may be improved by providing additional support and follow-up for participants at high risk of dropping-out and tailoring study requirements to participants' quality of life. Strengths of the current study include the exhaustive variable and function selection procedure to identify the health-related quality of life factor and its associational form to the odds of study completion. Further research is needed to assess whether the non-linear associations between the quality of life factors of pain and anxiety and the odds of study completion can be replicated in an independent, larger sample of endometrial cancer survivors receiving similar lifestyle intervention. In addition, conclusions drawn from this study only suggest possible associations between the quality of life factors and study completion. A randomized, controlled study is needed to draw and causative conclusions between the quality of life factors and study completion.

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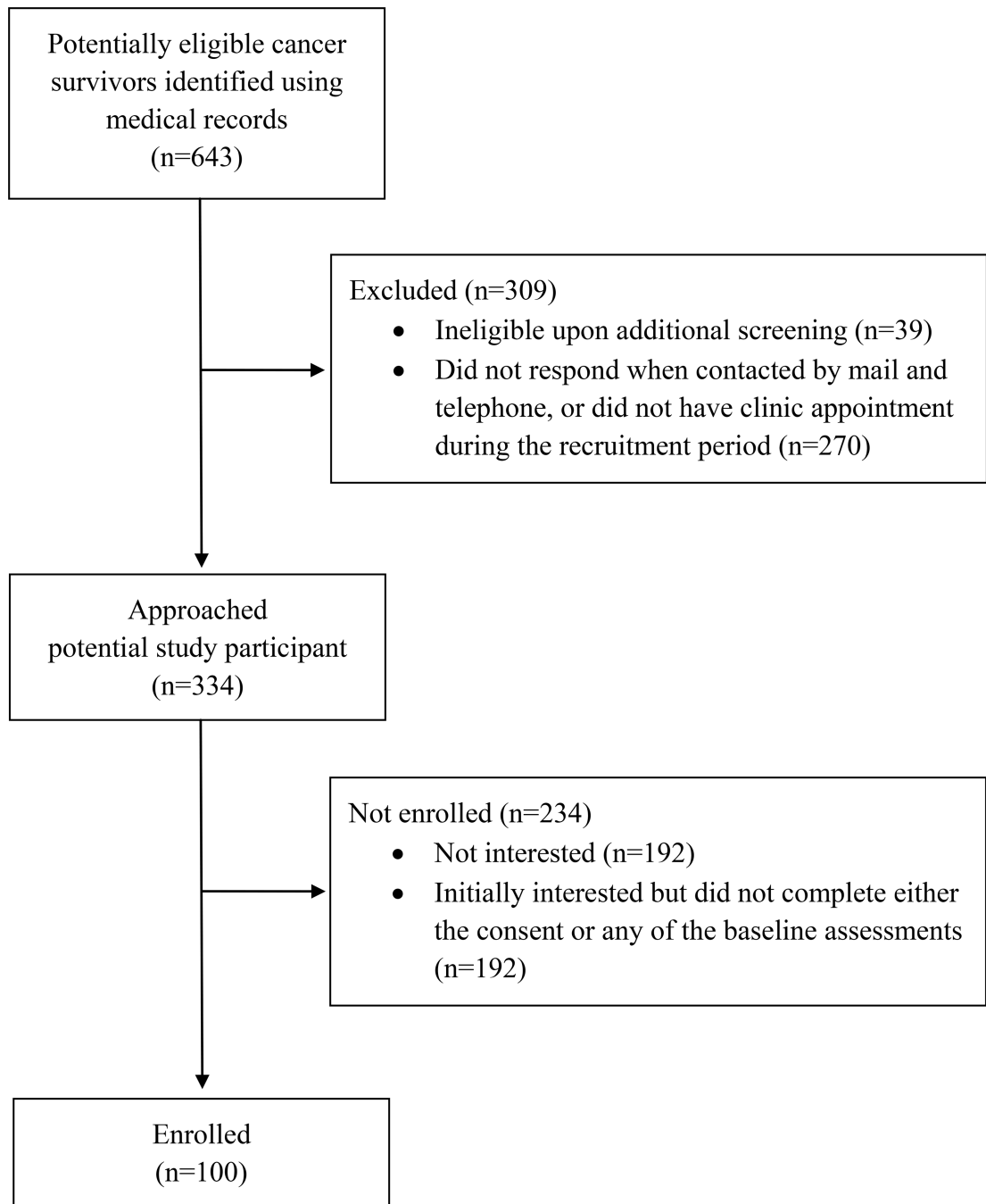


Figure 1.
Consort diagram.

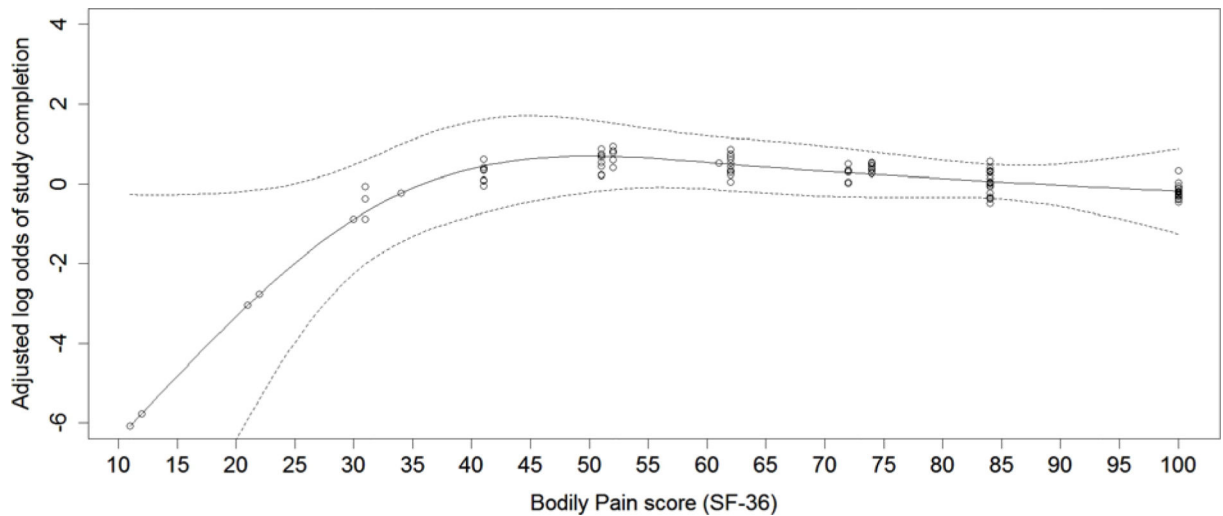


Figure 2.

Association between bodily pain (SF-36) and study completion.

Note 1: Circles in the plots represents predicted values based on the observed data. Multiple individuals had same subscale score: individuals with the same subscale score have the same predicted values on the estimated smoothed function. To visualize the number of observations across the subscale score range and to prevent overlapping values due to same subscale score, values were jittered by adding random noise.

Note 2: Solid line represents the estimated function from GAM, when adjusted for covariates of race (dichotomized as non-Hispanic whites vs. other) and disease stage (dichotomized as disease stage I vs. higher).

Note 3: The dotted lines represent 95% confidence bands.

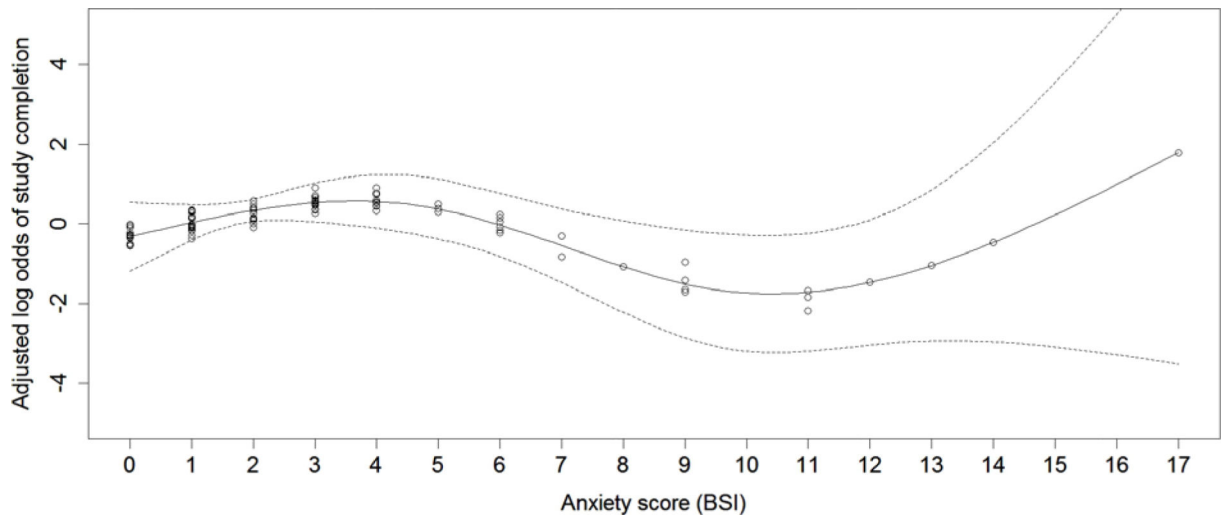


Figure 3.

Association between anxiety (BSI) and study completion.

Note 1: Circles in the plots represents predicted values based on the observed data. Multiple individuals had same subscale score: individuals with the same subscale score have the same predicted values on the estimated smoothed function. To visualize the number of observations across the subscale score range and to prevent overlapping values due to same subscale score, values were jittered by adding random noise.

Note 2: Solid line represents the estimated function from GAM, when adjusted for covariates of race (dichotomized as non-Hispanic whites vs. other) and disease stage (dichotomized as disease stage I vs. higher).

Note 3: The dotted lines represent 95% confidence bands.

