Published in final edited form as:
Psychooncology. 2010 May ; 19(5): 517–524. doi:10.1002/pon.1614.

Physical and Mental Health Correlates of Pregnancy Following Breast Cancer

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Abstract

Introduction—The safety of pregnancy after breast cancer is an important issue for many younger breast cancer survivors and their health care providers. Current research does not indicate that pregnancy negatively affects survival, but the "healthy mother bias," suggesting that survivors who go on to become pregnant are a self-selected healthier group based on their prognosis, has led to cautious interpretation of these findings. No studies have systematically evaluated the potential for this bias.

Methods—This nested case-control study includes 81 younger participants from the Women's Healthy Eating and Living Study (WHEL) (N=3088). Our sample includes 27 cases who had children after breast cancer and 54 controls, matched on age and stage at diagnosis. We used hierarchical linear modeling to accommodate longitudinal data with individuals nested within matched sets (cases and controls). The primary aim was to evaluate the association between summary scores of health and childbearing after breast cancer. Covariates were added for adjustment and to improve model precision.

Results—Controlling for other variables in the model, physical health scores were not different between cases and controls (B=0.14, p=0.96). Mental health scores were marginally higher among cases (B=6.40, p=0.08), as compared to controls, a difference considered clinically significant.

Conclusion—This preliminary study did not find evidence of a healthy mother bias based on physical health. However, mental health was 6 points higher (p=0.08) among those who had children, indicating that the role of mental health needs evaluation in future research. Larger studies are needed to verify these findings.

INTRODUCTION

A quarter of breast cancer cases in the United States are diagnosed in premenopausal women [1], about 5% of those in women younger than 40 [2]. It is estimated that about 250,000 women under the age of 40 are currently living with breast cancer [3]. Younger women have a unique set of concerns when faced with this diagnosis, especially those who may want to have a child. While younger survivors are more likely to be interested in having children, they may worry about whether or not it is safe [4]. One concern is that hormonal changes during pregnancy could have an adverse affect on the course of breast cancer [5,6]. The majority of research on pregnancy among breast cancer survivors has focused on its potential impact on mortality with

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most showing no harm and some suggesting it may be protective. [7–11]. Studies have failed to find significantly different outcomes for those who conceive after breast cancer compared to those who do not [10,12]. A review of the data found no published studies reporting decreased survival associated with subsequent pregnancy [13]. On the contrary, there is evidence that women who become pregnant after breast cancer have a lower relative risk of death compared to those who do not [7,9,11,12,14]. Women are usually advised to wait at least two to three years before conceiving since this is when recurrence is most likely, particularly for those with ER negative receptor status. However there is minimal evidence that waiting is necessary [9,15].

While pregnancy after breast cancer appears safe, several researchers have questioned the strength of available evidence. Limitations in current research include small sample sizes, reliance on limited data sources, such as cancer registry data, and selection and recall biases [13,16,17]. Key among these is the selection bias termed the “healthy mother bias,” which suggests that breast cancer survivors who go on to become pregnant are a self-selected, healthier group based on their prognosis [11]. Without additional information about the health of survivors who go on to have a child and those who don’t, researchers have been unable to verify this bias or control for potentially important health characteristics in their analyses. Subsequent pregnancies after breast cancer have also not consistently been tracked or reported [6,13].

The limitations in current research leave younger survivors and their health care providers with insufficient information to make decisions and recommendations about pregnancy. The potential for the healthy mother bias has been described as a key limitation in current research exploring the effect of pregnancy on long-term survival [11]. Our aim was to begin exploring this bias by providing some descriptive, preliminary evidence about the health characteristics of younger survivors who go on to have successful pregnancies after breast cancer as compared to those who do not. This nested case-control study is an evaluation of physical and mental health characteristics among 27 younger breast cancer survivors who had a child after treatment compared to 54 controls (matched on age at diagnosis and cancer stage) who did not. The purpose of this study was to evaluate whether mean health scores were higher among those who had a child, as the healthy mother bias suggests.

PATIENTS AND METHODS

Overview of the WHEL study

Participants for this study were identified from among participants in the Women’s Healthy Eating and Living (WHEL) study, a multi-site randomized controlled trial to evaluate the effectiveness of a high-vegetable, low-fat diet to reduce recurrence of breast cancer and early death. The WHEL study enrolled 3,088 women diagnosed between the ages of 18 and 70 who had completed initial treatment for early stage breast cancer. According to the accepted staging principles at the time of enrollment [18], approximately 40% of WHEL participants were diagnosed with Stage I (≤1cm), 55% with Stage II, and 5% with Stage IIIA breast cancer within the previous four years. Exclusion criteria included pregnancy at the time of enrollment. Other inclusion and exclusion criteria are extensive and described elsewhere [19].

The WHEL study’s primary outcomes were breast cancer recurrence and death from any cause. Outcome assessments were based on self-report every six months and researchers reviewed medical records to provide verification. Participants were followed from the date of study entry until the date of last follow-up or death. Participants who had a recurrence were encouraged to stay in the study.

The WHEL study enrolled participants between 1995 and 2000. The average age at study entry was 53.3 years and 376 (12.2%) of participants were 40 or younger at diagnosis. Over 85% of study participants were White. The results of the study were published in 2007 [20]. Over the mean 7.3-year follow-up, 256 women in the intervention group (16.7%) and 262 in the comparison group (16.9%) experienced an invasive breast cancer event. There were 155 deaths in the intervention group (10.1%) compared to 160 deaths in the comparison group (10.3%). Forty five percent of participants were enrolled 2–4 years post-diagnosis, so WHEL recurrence rates are likely more reflective of later recurrence.

Nested Case-Control Study Inclusion and Exclusion Criteria

This nested case-control study includes 81 WHEL participants; 27 cases who reported having a child during their study participation and 54 matched controls that did not. All participants were diagnosed with Stage I or Stage II invasive breast cancer between the ages of 26 and 40. Cases included only those who became pregnant after their enrollment into the WHEL study, rather than between diagnosis and study entry, to ensure that baseline measures were taken prior to pregnancy. Cancer stage was an exact match and age at diagnosis was the closest match within four years. The mean age difference at diagnosis between cases and controls was just under 12 months and 75% of participants were matched within 18 months. The potential pool of matched controls included those who: 1) had not had a child since their breast cancer diagnosis, 2) had the potential to become pregnant at the time of study entry, 3) completed at least one survey evaluating physical and mental health, and 4) were 40 or younger at diagnosis. Exclusion criteria included: 1) age at menopause is less than/equal to age at diagnosis, 2) postmenopausal at baseline, 3) hysterectomy at baseline, and 4) bilateral oophorectomy at baseline. These criteria were chosen to identify a control group with the potential to become pregnant at study baseline. Recurrence and survival outcomes were not considered as part of the inclusion/exclusion or matching criteria.

Measures

The criterion variables in this analysis, physical health summary score (PHSS) and mental health summary score (MHSS), were taken from the RAND 36 item health survey (SF-36). The survey was administered at five time points over the course of the WHEL study: baseline, 12, 24 or 36 (split sample- 50% at each time point), 48, and 72 months. Questionnaires were administered at baseline and mailed prior to each clinic visit.

Responses from the SF-36 are categorized into four mental health (mental health index, vitality, role limitations due to emotional problems, and social functioning) and physical health (physical functioning, general health perceptions, bodily pain, and role limitations due to physical health problems) sub-scales. The mental and physical health dimensions are consolidated into two separate scores, the MHSS and PHSS [21,22]. The SF-36 has been used extensively in other research involving women with breast cancer (alpha=0.75–0.91) [23–26]. Using WHEL study baseline data (N=2,999), coefficient alpha was good to excellent (0.93 SF-36, 0.93 PHSS, and 0.89 MHSS). Responses are scored 0–100, where higher scores equal improved health. A difference of 5 points is considered clinically meaningful [22].

Having a child after breast cancer was the primary predictor of physical and mental health scores. Births were identified through an extensive review of existing WHEL study data, including reported hospitalizations, reported number of children at baseline and exit interviews, and review of written participant notes throughout the study. Two researchers completed an independent review of the data to identify cases and came to a consensus.

Statistical Analyses

We first characterized the sample using descriptive statistics for the entire sample and stratified by case-control group (Table 1). We assessed possible baseline differences between groups using conditional logistic regression to control for matching. We identified potential covariates by evaluating differences in PHSS and MHSS across individual variables using bivariate analyses. We added potential covariates to the initial model ($p<0.25$) and retained significant covariates ($p<0.10$) for adjustment and improved precision. Variables listed in Table 1 were added in the following order: demographics, lifestyle, reproductive history, and cancer characteristics and treatment. To control for demographic characteristics, race/ethnicity and marital status were retained in all models. We then evaluated the residual distribution of each outcome. With PHSS as the criterion variable, it was necessary to remove four (of a possible 156 data points) extreme outliers to meet the normality assumption required for SAS Proc Mixed. For the MHSS analysis, two data points were removed.

The primary aim of this study was to assess whether or not there was a mean difference in PHSS or MHSS between women who had a child after breast cancer (cases) compared to a matched group who did not (controls). Hierarchical linear modeling (HLM) using SAS Proc Mixed was used to analyze a data structure of participants with repeated measures nested within groups of matched sets (cases and controls). The first analysis evaluated the association between PHSS (level-1 criterion variable) and childbearing after breast cancer (level-2 predictor variable). Model testing was conducted in 2 phases: 1) an unconditional, intercept-only model was developed to calculate the intra-class correlation (ICC) to identify the percent of variability in PHSS between individuals and across time periods and 2) a 3-level means-as-outcome model [27] was developed to accommodate longitudinal data with individuals nested within matched sets. Level-2 covariates were added to the initial model based on preliminary analyses of an association with the primary criterion variable ($p<.25$). Ages at diagnosis and cancer stage were matching criteria and were not included in the model. The primary criterion variable, demographic variables, and covariates that were significantly associated with the primary criterion variable ($p\leq.10$) were retained in the final model. We followed the same procedure with MHSS as the criterion variable. Due to small sample size, we did not evaluate random effects.

For cases, we used only data collected prior to the probable time of pregnancy based on when the child was born. For controls, we censored available data so that each matched control had data only up to the last point of data collection for the matched case. Among the 54 controls, 33 had 1 data point, 6 had 2 data points, 11 had 3 data points, 3 had 4 data points, and 1 had 5 data point. Among the 27 cases, 13 had 1 data point, 2 had 2 data points, 5 had 3 data points, 6 had 4 data points and 1 had 5 data points. HLM accounts for correlations of observations within subjects and within matched sets, accommodates missing data, and allows inclusion of data from all available measurement periods.

RESULTS

Sample Characteristics

The sample includes 81 participants, 27 cases and 54 controls matched on cancer stage and age at diagnosis (Table 1). Approximately the same percentage of cases and controls were in the WHEL intervention and control arms, with no significant differences in recurrence or survival rates between groups. Though cases and controls were matched on age within 4 years, controls were slightly older at study entry (34.4 years compared to 33.9 years for cases, $p=0.06$). Cases were also marginally significantly more educated ($p=0.06$) and likely to be White ($p=0.09$). There were no significant differences in lifestyle or health behaviors. More cases had no previous children, though this was not statistically significant. Almost twice as many women in the control group had a mastectomy compared to cases. Although type of surgery was significantly different between groups, this variable was not associated with PHSS (p=0.57) or MHSS (p=0.47) in bivariate analyses and, therefore, was not included either in multivariate model.

Physical Health Summary Score (PHSS)

Without controlling for other variables, the mean PHSS across cases (85.5, 95%CI 81.4–89.6) and controls (81.3, 95%CI 78.2–84.3) were not significantly different (Table 2). The intercept-only model revealed an ICC of .48. Thus, 48% of the variance in PHSS was between-individuals, indicating that values were equally variable within persons across occasions and between persons. With only the primary level-2 predictor variable in the model, the regression coefficient relating childbearing to individual PHSS was positive and not statistically significant (B=4.61, p=0.15) (Table 3). Participant's PHSS was not significantly higher among those survivors who had children compared to those who did not. After adding demographic characteristics and significant covariates (p≤ 0.10) to the model, PHSS was not significantly higher in those who had a child after breast cancer (B=0.14, p=0.96) or those who were White (B=4.87, p=0.15). PHSS was significantly higher in those who were married (B=9.27, p=0.003) and those who were older at menarche (B=2.59, p=0.009). PHHS was significantly lower among those with higher BMI at baseline (B=−0.78, p=0.005) and those with a recurrence during the study (B=−6.23, p=0.04).

Mental Health Summary Score (MHSS)

The mean MHSS for cases (81.7, 95%CI 77.2–86.2) was significantly higher than for controls (72.5, 95%CI 68.9–76.1) prior to controlling for other variables (Table 2). Similarly to the PHSS model, the intercept only model for MHSS indicated that values were equally variable within persons across occasions and between persons (ICC= 0.49). With only the primary predictor variable in the model, the regression coefficient relating childbearing to individual MHSS was positive and statistically significant (B=7.79, p=0.04) (Table 4). After adding demographic characteristics and significant covariates (p≤ 0.10), MHSS was marginally significantly higher in those who had a child after breast cancer (B=6.40, p=0.08) and those who were married (B=7.14, p=0.08). MHSS did not vary by race/ethnicity (B=−4.36, p=0.33). MHSS was significantly lower among those with higher BMI (B=−0.82, p=0.02).

DISCUSSION

The healthy mother bias is a selection bias that may result when women who have better prognoses go on to have successful pregnancies. In an attempt to account for this possibility, survival analyses have controlled for age and cancer stage at diagnosis. However, this may inadequately address potential health differences between groups, including aspects of physical and mental health. Among WHEL study participants, for example, physical health summary scores significantly predict breast cancer recurrence [28]. We conducted this study to further explore the physical and mental health of younger breast cancer survivors who had successful pregnancies compared to a group who did not, matched on cancer stage and age at diagnosis. Multi-level analysis did not identify a difference in physical health scores between those who became pregnant and those who did not. This indicates the lack of a healthy mother bias based on physical health among our sample. Our findings suggest that this bias may not impact on current research evaluating the association between survival and childbearing after breast cancer. However, this study is preliminary and needs to be verified in larger studies. We did find a marginally significant difference in mental health; those who went on to become pregnant appeared to have higher scores. While mental health has not been traditionally identified as a component of the healthy mother bias, it is possible that mental health is part of a "healthy mother" and needs to be considered.

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Unlike previous studies, we compared cases and controls across several variables and included key covariates in a multi-level model. Results of conditional multivariate modeling showed that the PHSS between these groups were very similar. However, women who had children after breast cancer had pre-pregnancy mental health scores that were about 6 points higher than those who did not (p=0.08). Our study did not have sufficient power to detect a statistically significant difference, but this finding suggests that those who had children had improved mental health (a 5-point difference is considered clinically meaningful) [22]. Although this preliminary study cannot determine causality, it is possible that those women with better mental health, including lower levels of stress and anxiety, improved social and emotional functioning, better support, and higher energy, were more likely to have successful pregnancies. Research on the link between psychosocial functioning and fertility is mixed [29–31], with some studies reporting an association between psychosocial variables and reproductive status [e.g. 32,33] and other studies reporting no link [e.g. 34,35]. It is also possible that those with improved mental health would be more likely to desire children based on factors such as an expectation of long-term survival, a strong family life, and the availability of a support system. Other researchers have found that some women who survive breast cancer experience an intensified desire for children in order to feel normal and have the positive experience of having a child. Women's negative motivations may also be strengthened by fears related to health and the long-term well being of themselves and their children [36–38]. Adverse treatment outcomes, such as premature menopause, infertility and fertility concerns, have also been associated with poorer QOL scores [39–41]. It is possible that those who had difficulties with fertility had lower scores, though we were unable to evaluate this in the current study due to lack of data on attempted pregnancy. Future studies evaluating pregnancy outcomes should include an assessment of pregnancy intentions and factors influencing those decisions to better understand the differences between women who have children after breast cancer and those who do not.

QOL, as measured by the SF-36, encompasses self-reported physical and psychosocial well-being within the context of one's experiences with disease, but it is not age, disease or treatment specific [42]. QOL scores among cancer survivors have not previously been explored as indicators of physical and mental health prior to pregnancy. One study explored QOL after pregnancy among a small group of younger breast cancer survivors, but found no significant differences between those who had children and those who did not [43]. The current study found relatively high mean scores in both the physical (81.3, 85.5) and mental health (72.5, 81.7) domains, with controls having lower overall scores. In previous analyses with WHEL participants (N=2,582), QOL scores were generally high and comparable to the norms for women in the general population and others with breast cancer [26].

There were no significant differences in demographics or lifestyle between cases and controls, and health behaviors that would likely influence overall health, such as diet and tobacco use, were similar between groups. The vast majority of both cases (92.6%) and controls (96.3%) received chemotherapy, indicating aggressive treatment. While the percentage of women with radiation and chemotherapy was similar across groups, a significantly larger portion of cases had a lumpectomy rather than a mastectomy. This cannot be explained by a difference in cancer stage, since this was a matching criterion. There are many potential reasons for this disparity, including medical history, physician recommendations, and personal choices. Further study is needed to identify factors that may influence cancer treatment and surgical choices among younger women.

This study is the first to systematically evaluate differences in physical and mental health among a group of young breast cancer survivors who had children after their diagnosis compared to those who did not. Typical of studies focused on pregnancy after breast cancer, the primary limitation of this study is small sample size, which restricted our ability to detect statistically significant differences between groups. Also, because of the small sample of young participants, we were not able to match on exact age and those in the case group are slightly, though not significantly, younger than controls. We had a smaller amount of data for our analyses because we restricted our dataset to pre-pregnancy time points for each matched set. However, the multilevel modeling technique allows for unbalanced data sets and missing data. Although extensive effort went into identifying cases, it is possible that some women were miscategorized. In addition, all participants in this study were diagnosed with early-stage breast cancer and cases became pregnant after treatment ended and during study participation (enrolled within 4 years post-diagnosis). Our findings are limited to these groups. Finally, the WHEL study did not collect participant's full reproductive history, including attempted pregnancy or pregnancies that were terminated spontaneously or therapeutically. Therefore, we could not evaluate attempted pregnancy in our control group or control for reproductive history in our analyses. That issue is beyond the scope of this study, but is important for future investigation.

Younger women represent a minority of breast cancer cases, but many young survivors are interested in the possibility of pregnancy [4,36,44,45]. Those who want to have children need to know the potential risks. Information to help younger breast cancer survivors make important reproductive decisions is sparse and patient-provider communication on these issues is limited [4,46–48]. Current research does not indicate that women should avoid pregnancy after breast cancer. However, selection and recall biases, such as the healthy mother bias, have resulted in cautious interpretation of these findings. This is the first study to investigate this bias. While our small sample size restricted our ability to detect statistical significance, physical health scores were very similar between groups and we found no evidence of a healthy mother bias. This provides preliminary evidence that previous research indicating the safety of pregnancy may not be significantly impacted by this bias. This holds particularly true for those with early stage breast cancer who become pregnant after treatment ends. In addition, mental health, while not traditionally discussed in the context of this bias, was marginally significantly better among women who had children. Mental health is an important component of overall health and our findings indicate that its relationship to post-cancer pregnancy should be evaluated in future studies. Evaluation of the association between mental health, attempted pregnancy, and pregnancy outcomes would further clarify these findings.

Acknowledgments

This study was initiated with the support of the Walton Family Foundation and continued with funding from NCI grants CA 69375 and CA 72092. Some of the data were collected from the General Clinical Research Centers, NIH grants M01-RR00070, M01-RR00079, and M01-RR00827.

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Table 1

Descriptive characteristics at baseline by case-control status (N=81)

	Cases (n=27)		Controls (n=54)		p-value*
	N (%)	Mean (SD)	N (%)	Mean (SD)	
WHEL study participation					0.75
Intervention	12 (44.4)		22 (40.7)		
Control	15 (55.6)		32 (59.3)		
Demographics					
Age at study entry (Mean, SD)		33.9 (3.8)		34.4 (3.2)	0.06
Age at diagnosis					1.00
30–34	20 (74.1)		40 (74.1)		
35–40	7 (25.9)		14 (25.9)		
Education level					0.06
Less than college grad	7 (25.9)		26 (48.1)		
College grad or higher	20 (74.1)		28 (51.9)		
Race/ethnicity					0.09
White, non-Hispanic	24 (88.9)		40 (74.1)		
Other	3 (11.1)		14 (25.9)		
Marital status					0.13
Married	23 (85.2)		38 (70.4)		
Single/Other	4 (14.8)		16 (29.6)		
Health insurance					1.00
Private/Military	27 (100)		52 (96.3)		
None/Unknown	-		2 (3.7)		
Lifestyle					
BMI (Mean, SD)		23.4 (3.8)		24.8 (5.9)	0.28
Dietary guidelines met[1]					0.87
Meets 0–1		19 (70.4)		37 (68.5)	
Meets 2–3		8 (29.6)		17 (31.5)	
Physical activity [2] (Mean, SD)		973.2 (896.0)		1030.8 (1110.3)	0.82

	Cases (n=27)		Controls (n=54)		p-value*
	N (%)	Mean (SD)	N (%)	Mean (SD)	
Smoking	-----			-----	0.21
Current					
Ever	10 (37.0)			12 (22.2)	
Never/Unknown	17 (63.0)			42 (77.8)	
Reproductive history					
No. live births at study entry					0.22
0	14 (51.9)		21 (38.9)		
1 or more	13 (48.1)		33 (61.1)		
No. pregnancies at study entry					0.57
0	10 (37.0)		17 (31.5)		
1 or more	17 (62.9)		37 (68.6)		
Age at first live birth (Mean, SD)		28.6 (5.1)		26.5 (4.2)	0.08
Age at menarche (Mean, SD)		13.0 (1.6)		12.6 (1.2)	0.13
Cancer characteristics and treatment					
Mother with breast cancer	6 (22.2)		5 (9.3)		0.10
Cancer stage at diagnosis					1.00
Stage I	6 (22.2)		12 (22.2)		
Stage II	21 (77.8)		42 (77.8)		
Receptor status					0.48
ER+/PR+ and ER+/PR−	20 (80.0)		36 (69.2)		
ER−/PR−	5 (20.0)		16 (30.8)		
Radiation	19 (70.4)		29 (53.7)		0.14
Chemotherapy	25 (92.6)		52 (96.3)		0.49
Lumpectomy	19 (70.4)		21 (38.9)		0.01
Mastectomy	8 (29.6)		33 (61.1)		0.01
Tamoxifen use					0.32
Never used at baseline	18 (69.2)		30 (56.6)		
Previous/current use	8 (30.8)		23 (43.4)		
Any recurrence	8 (29.6)		15 (27.8)		0.86

	Cases (n=27)		Controls (n=54)		p-value*
	N (%)	Mean (SD)	N (%)	Mean (SD)	
Survival	24 (88.9)		47 (87.0)		0.80

*Conditional logistic regression, adjusted for matching

[1] Based on National Cancer Institute daily dietary recommendations. 1 point for each recommendation met: ≤30% energy from fat, ≥20g fiber, ≥ 5 servings fruit/vegetables

[2] Metabolic equivalents per week

Table 2

Mean physical health summary score (n=152) and mental health summary score (n=154) across observations

Physical health summary score*					
Case			**Control**		
Mean	SE	95% CI	Mean	SE	95% CI
85.49	2.08	81.38–89.60	81.27	1.53	78.24–84.30

Mental health summary score*					
Case			**Control**		
Mean	SE	95% CI	Mean	SE	95% CI
81.70	2.29	77.19–86.22	72.46	1.83	68.85–76.07

*Scores range from 0–100, where higher scores equal improved health

Table 3

Results of fitting models to physical health summary score data (n=152)

Variable	Unconditional Model Estimate (SE)	p-value	Conditional Univariate Model Estimate (SE)	p-value	Conditional Multivariate Model [a] Estimate (SE)	p-value
Intercept	82.83 (1.52)	<0.001	81.19 (1.88)	<0.001	82.58 (1.67)	<0.001
Case/Control			4.61 (3.14)	0.15	0.14 (2.74)	0.96
Ethnicity (Ref= Non-White)					4.87 (3.38)	0.15
Marital status (Ref= Not married)					9.27 (3.03)	<0.01
BMI					−0.78 (0.27)	<0.01
Age menarche					2.59 (0.98)	<0.01
Recurrence (Ref= No recurrence)					−6.23 (3.01)	0.04

* All level-2 covariates are centered on the sample mean except case/control status. The intercept represents a control with an average value of ethnicity, marital status, BMI, age at menarche, recurrence.

Table 4

Results of fitting models to mental health summary score data (n=154)

Variable	Unconditional Model Estimate (SE)	p-value	Conditional Univariate Model Estimate (SE)	p-value	Conditional Multivariate Model* Estimate (SE)	p-value
Intercept	75.31 (1.84)	<0.001	72.58 (2.23)	<0.001	73.17 (2.14)	<0.001
Case/Control			7.79 (3.74)	0.04	6.40 (3.67)	0.08
Ethnicity (Ref= Non-White)					−4.36 (4.48)	0.33
Marital status (Ref= Not married)					7.14 (4.02)	0.08
BMI					−0.82 (0.35)	0.02

*All level-2 covariates are centered on the sample mean except case/control status. The intercept represents a control with an average value of ethnicity, marital status and BMI.