Brain, Behavior, & Immunity - Health 10 (2021) 100180

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx

Full Length Article

Behavioural, physical, and psychological predictors of cortisol and C-reactive protein in breast cancer survivors: A longitudinal study

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ARTICLE INFO

Keywords:
Breast cancer
Cortisol
C-reactive protein
Predictors
Multilevel modeling

ABSTRACT

Background: Breast cancer survivors (BCS) can exhibit a dysregulation of cortisol and elevated C-reactive protein (CRP) levels post-treatment, which increase the risk of diverse health outcomes. Certain behavioural, physical, and psychological variables may help to predict cortisol and CRP levels post-treatment. The aims of this study were to: (1) describe naturally occurring changes in absolute diurnal cortisol and CRP levels over a period of 1.5 years post-treatment among BCS, (2) assess if absolute diurnal cortisol and CRP levels change in tandem, and (3) assess behavioural, physical, and psychological variables as predictors of absolute diurnal cortisol levels and CRP levels.

Methods: Capillary blood and saliva samples were collected from 201 BCS, on average, 3.5 months post-treatment (T1) and again 3, 6, 9, and 12 months later (T2–T5). At each time point, five saliva samples were collected on two nonconsecutive days: at awakening, 30 min after awakening, 2:00 p.m., 4:00 p.m., and at bedtime. At each time point, participants also completed self-report questionnaires and wore an accelerometer for seven consecutive days. Data were analyzed using multilevel modeling.

Results: Absolute diurnal cortisol levels did not change significantly over time. CRP levels decreased across time points ($B_{linear} = -0.31$, $p = .01$), though the rate of decrease slowed over time ($B_{quadratic} = 0.05$, $p = .03$). Generally, greater sedentary time predicted higher overall absolute diurnal cortisol levels ($B < 0.01$, $p = .01$); whereas higher physical activity ($B = -0.004$, $p < .01$), lower body mass index ($B = 0.10$, $p < .01$), and lower health- and cancer-related stress ($B = 0.24$, $p = .04$) predicted lower overall CRP levels. Also, lower absolute diurnal cortisol levels were evident when participants engaged in more sedentary time, as compared to their own average sedentary time ($B = -0.01$, $p < .01$).

Conclusions: Results offer insight into the nature of change in diurnal cortisol and CRP levels among BCS from treatment completion onwards and offer clinical implications. Helping BCS manage their weight, reduce stress, increase physical activity participation, and decrease sedentary time as soon as possible after treatment may help to reduce physiological dysregulations, thereby lowering the risk of adverse health outcomes in this population. Further research investigating specific intervention parameters such as type, context, frequency, and intensity are warranted for the development of the most optimal interventions.

1. Introduction

Experiencing stress due to cancer and its treatment can negatively influence people's psychological and physical health (Selye, 2013). For example, long-term prolonged stress had been linked to depression and serious health risks such as obesity and heart diseases in non-clinical (da Estrela et al., 2020; Miller and Blackwell, 2006) and clinical populations (Coughlin, 2011; Maass et al., 2015). In response to stressful life events (e.g., cancer diagnosis), the human body releases stress hormones like adrenaline and cortisol. In the short-term, these hormones are helpful because they can increase a person's ability to respond to a stressor, while they generally return to normal levels once the stressful situation has passed (Slavish et al., 2015). However, in the long-term, when stress is chronic, the body's production of stress hormones becomes dysregulated,

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https://doi.org/10.1016/j.bbih.2020.100180
Received 15 September 2020; Received in revised form 26 November 2020; Accepted 28 November 2020
Available online 1 December 2020
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thereby impeding a return to normal (McEwen, 1998; Miller et al., 2007). Over time, these hormones can lead to physiological changes and cause serious health problems (McEwen, 1998, 2008; Selye, 2013). For instance, chronic stress may lead to either elevated or below normal cortisol levels and both types of dysregulations can have important negative effects on health (Herriot et al., 2020; McEwen, 2008; Miller et al., 2007). Dysregulation of cortisol levels may in turn prompt an increase in circulating C-reactive protein (CRP) levels, a marker of systemic inflammation (Gouin et al., 2012; Rueggeberg et al., 2012; Slavish et al., 2015). These physiological dysregulations have been linked to several negative health outcomes such as increased disability and reduced longevity (Reza et al., 2014; Schrepf et al., 2013; Sharpley et al., 2019).

Although there are data showing that breast cancer survivors (BCS) feel stressed (Allen et al., 2008) and exhibit dysregulated cortisol and elevated CRP levels post-treatment (Hsiao et al., 2017; Wiley et al., 2017), studies are needed to explore the long-term effects of chronic stress on cortisol and CRP levels once treatment ends. Findings suggest that dysregulated cortisol and elevated CRP levels in BCS tend to normalize and have a trend towards recovery with the passage of time followed the end of treatment (Couture-Lalande et al., 2014; Hsiao et al., 2017; Villasenor et al., 2014; Wiley et al., 2017; Zeitzer et al., 2016). Though these existing studies are informative, little is known about *how* cortisol and CRP levels change over time post-treatment. Studies assessing trajectory of changes and predictive variables are needed to gain a better understanding of the long-term physiological outcomes of an experience of breast cancer, and identify women at greater risk of dysregulations. Physiological disturbances are concerning in BCS, given that cortisol and CRP can exert downstream implications on general health and play an essential role in a person's ability to regulate stress and fight infections and injuries (Asegaonkar et al., 2015; Miller et al., 2007).

1.1. The role of behavioural and psychological variables in the physiological outcomes of BCS

Andersen's (1994) biobehavioural model suggests that a diagnosis of cancer and its treatments generate a significant level of stress and alter quality of life thereby leading to behavioural and psychological responses, which in turn influence physiological processes. More specifically, the model proposes that the stress caused by a cancer experience increases engagement in poor health behaviours such as unhealthy diet and drug use (e.g., alcohol, nicotine), and reduce initiation of positive health behaviours such as physical activity (PA). This can in turn produce changes in survivors' physiology (Andersen et al., 1994). Since the development of the model, accumulating evidence has supported a general conclusion that various behavioural, physical, and psychological variables might predict the physiological outcomes of cancer survivors (Hsiao et al., 2017; Villasenor et al., 2014). Examining predictors of cortisol and CRP levels in BCS guides the development of targeted health interventions.

Our team previously examined socio-demographic, health-, and cancer-related predictors of absolute diurnal cortisol and CRP levels in BCS (Lambert et al., 2020). Results showed that: (1) absolute diurnal cortisol and CRP levels fluctuate over time, (2) older age and post-menopausal status are associated with higher absolute diurnal cortisol and CRP levels, (3) more advanced cancer stages and chemotherapy exposure are associated with lower absolute diurnal cortisol levels, and (4) being overweight/obese is associated with higher CRP levels. Although these findings help to identify women who may be at greater risk of post-treatment physiological dysregulations, these factors are largely non-modifiable. Examining *contributing* and *modifiable* factors is still needed to help select appropriate intervention strategies to promote optimal health outcomes in BCS. Moreover, our extant work employed an analytical technique that treats clustering that occurs because repeated observations are nested within participants as nuisance (i.e., repeated and mixed analyses of variance). Considering that multilevel modeling (MLM) views such clustering as a feature of the data and one that is of substantive interest (Sherry and MacKinnon, 2013), it may provide a more sophisticated approach to examining predictors in a longitudinal study. Additionally, MLM allows researchers to consider continuous candidate predictors (rather than categorical) and intra- and inter-individual component in the associations between predictors and physiological outcomes, whereas conventional approaches focus on the inter-individual component solely. Consideration of both intra- and inter-individual level associations is necessary as observing an inter-individual level association does not guarantee a similar intra-individual level association and vice versa, and associations at both levels have different implications for the design of interventions (Hox, 2010). Specifically, intra-individual level associations help to identify which factors have the potential to elicit individual change (and thus the most effective elements worth targeting in interventions), whereas inter-individual level associations help to identify who is at greater risk. Thus, using MLM to examine contributing and modifiable factors associated with cortisol and CRP levels would help not only to remedy limitations of conventional analytical approaches, such as those employed by Lambert et al. (2020), but help to identify *who* would most likely benefit from interventions, along with *what* should be addressed in those interventions.

In another study (Sabiston et al., 2018a), our team found that: (1) BCS have lower CRP levels when they are more active (as compared to their average PA level), and (2) BCS who generally engage in more PA have lower average CRP levels as compared to BCS who generally engage in less PA. We consider these results important for two reasons. From a practical standpoint, they suggest that PA interventions might help mitigate adverse physiological dysregulations post-treatment. From a research standpoint, they imply that PA should be included in future analyses to account for its association with CRP levels when examining other predictive factors such as psychological health. Moreover, given the importance and prevalence of dysregulated cortisol levels post-treatment for cancer, the assessment of the association between PA and cortisol levels is also warranted.

1.2. The current study

In order to extend current knowledge on cortisol and CRP levels among BCS (Hsiao et al., 2017; Lambert et al., 2020; Sabiston et al., 2018a; Villasenor et al., 2014), the first objective of this study was to explore how absolute diurnal cortisol and CRP levels change over the first 1.5 year post-treatment using a MLM approach. Based on previous findings (Rutter et al., 2013), it was hypothesized that changes in CRP levels over time would be best described by a quadratic trend whereby a sharp decrease would be initially observed followed by a deceleration in decrease to a slow return to normative values. Given the different plausible associations between chronic stress and cortisol levels (Bower et al., 2005; Hsiao et al., 2017), no specific hypothesis was put forward for direction and form of change for absolute diurnal cortisol levels. Additionally, given that studies suggest that dysregulated cortisol levels might prompt the release of inflammatory markers such as CRP (Black, 2003; Slavish et al., 2015), the second objective of this study was to assess whether changes in CRP levels were predicted by initial and/or concurrent absolute diurnal cortisol levels. It was hypothesized that changes in CRP levels would be predicted by changes in cortisol levels.

Finally, in line with Andersen's (1994) biobehavioural model that highlights the importance of behavioural and psychological factors for health outcomes in cancer survivors, the third objective of this study was to identify modifiable time-varying variables that account for intra- and inter-individual differences in initial absolute diurnal cortisol and CRP levels (i.e., intercepts) as well as rate of change (i.e., slopes) in BCS over the first 1.5 year post-treatment. Variables included as candidate predictors were: sedentary time (ST), depressive symptoms, perceived general stress, and perceived health- and cancer-related stress. Moderate-to-vigorous intensity PA (MVPA) and body mass index (BMI) were also

included as candidate predictors considering the associations observed in our previous work (Lambert et al., 2020; Sabiston et al., 2018a) and to account for their variance in the estimated models. Consistent with findings in non-clinical population (Colbert et al., 2004; Howard et al., 2015; Kao et al., 2009; Shimanoe et al., 2014; Valkanova et al., 2013), it was hypothesized that higher ST and greater depressive symptoms and stress (general and health- and cancer-related) would predict higher CRP levels in BCS, both at the inter- and intra-individual levels. As for cortisol levels, although significant associations with ST, depression symptoms, and general and health- and cancer-related stress were expected, no directional hypothesis was put forward given the different patterns of findings in the literature (Miller et al., 2007).

2. Methods

2.1. Participants and procedures

Data analyzed for this study were drawn from a longitudinal study that aimed to examine BCS' lifestyle behaviours and their associations with physical and psychological health outcomes (Sabiston et al., 2018b). Briefly, participants were recruited through advertisements, word of mouth, and referrals from oncologists in different medical clinics and hospitals across Montreal, Quebec. Inclusion criteria were: (a) be at least 18 years of age, (b) have a previous diagnosis of stage I-III breast cancer, (c) be 0–20 weeks post-primary treatment (i.e., chemotherapy, radiotherapy, surgery), (d) be able and willing to provide informed consent, and (e) be able to read and speak English or French. Exclusion criteria were: (a) had received a previous diagnosis of cancer, and/or (b) have suffered from a health condition that may prevent PA.

The study protocol was approved by University and hospital research ethics committees. Once eligibility was confirmed, at approximately 3.5 months post-treatment (T1) and every 3 months thereafter (T2–T5), participants completed a self-report questionnaire package (to measure BMI, depressive symptoms, and stress levels) and wore an accelerometer for seven consecutive days (to measure ST and MVPA). At all time points (T1–T5), they were also asked to collect five saliva samples on two nonconsecutive days at awakening, 30 min after awakening, 2:00 p.m., 4:00 p.m., and at bedtime (to measure absolute diurnal cortisol levels) and provide a drop of capillary blood (to measure CRP levels). Participants were asked not to brush their teeth and engage in PA during the 30 min prior to the saliva collection. Saliva and blood samples were stored in participants' refrigerator and returned to the laboratory within 7 days in a biosafety bag. Once at the laboratory, samples were stored at −80° Fahrenheit until analysis.

2.2. Measures

2.2.1. Cortisol

Cortisol assays were analyzed in duplicate at the University of Trier, Germany, using a time-resolved fluorescence immunoassay with a cortisol–biotin conjugate as a tracer (Kirschbaum and Hellhammer, 2000). Areas under the curve with respect to ground (AUCg) cortisol levels were calculated for each of the two nonconsecutive days using the trapezoidal method. The mean AUCg for both days was computed for T1–T5 to provide a single summary represent absolute diurnal cortisol levels (Pruessner et al., 2003).

2.2.2. CRP

At T1–T5, a capillary whole blood drop was collected from participants' index or middle finger using a single-use lancet. Blood drops were collected on a Whatman protein saver card (VWR International, QC). All samples were analyzed at the Laboratory for Human Biological Research at Northwestern University using a high-sensitive enzyme immunoassay protocol (McDade, 2007).

2.2.3. ST and MVPA

At T1–T5, participants wore a GT3X accelerometer (Actigraph, Pensacola, Florida) on their hip during waking hours (except for periods of bathing/showering or other water activities) for seven consecutive days. Accelerometer data were downloaded in 60-sec epochs and daily min of ST ($<$ 100 counts•min^{-1}) and MVPA ($\geq$ 1952 counts•minute^{-1}) were calculated using established cut-points (Freedson et al., 1998), while controlling for the number of days and hours the accelerometer was worn. Daily ST and MVPA min were summed across the 7-day period to obtain total weekly ST and MVPA min. Accelerometer data were included in the analysis if there were no extreme counts ($>$ 20,000) and if participants wore the device for at least 4 days for a minimum of 600 min per day (Troiano et al., 2008).

2.2.4. BMI

At T1–T5, participants self-reported their weight and height, and BMI was calculated as weight in kilograms divided by height in meters squared.

2.2.5. Depressive symptoms

At T1–T5, participants completed a self-reported questionnaire package including the 10-item version of the Centre for Epidemiological Studies Depression Scale (CES-D; Andresen et al., 1994). The CES-D inquires about the frequency to which 10 symptoms were experienced during the past week (7 days) using a scale ranging from 0 (*rarely* or *none of the time*; $<$1 day) to 3 (*all the time*; 5–7 days). After reverse scoring positively worded items, average scores were computed, whereby higher scores represent greater frequency of depressive symptoms.

2.2.6. Perceived general stress and health- and cancer-related stress

At T1–T5, participants completed the Perceived Stress Scale (PSS; Cohen and Williamson, 1988) and the revised 5-item Assessment of Survivors Concerns (ASC) scale (Gotay and Pagano, 2007). The PSS is a general measure of perceived stress and includes 10 items measuring participants' perception of how uncontrollable, unpredictable, and overwhelming their life had been over the last month on a scale ranging from 1 (*never*) to 5 (*very often*). The ASC scale comprises two subscales, namely a general health worry subscale (includes fear of dying and health status in general) and a cancer worry subscale (includes fear about future tests, new cancer, and recurrence), with responses ranging from 1 (*not at all*) to 4 (*very much*). After reverse scoring negatively worded items for the PSS, average scores for PSS and the ASC scale were computed, where higher scores indicate greater general stress and greater health- and cancer-related stress, respectively.

2.3. Data preparation and analyses

Data were analyzed using SPSS (version 26; IBM Corp, Armonk, NY, USA). The level of statistical significance was set to $p < .05$. All data handling described below were performed in line with strategies advised by Bauer and Curran (2016). Prior to the main analyses (i.e., MLM), data were examined for accuracy of entry, patterns of missing data, potential outliers, and model assumptions. Because one of the important advantages of MLM is that it allows for the analysis of incomplete repeated measures data without restrictive assumptions on the covariance matrix, all Level-1 variables with at least one available time point were included in the analyses and missing data were not replaced.

For the main analyses, a series of longitudinal multilevel models which had a multilevel structure with five repeated measures nested within participants were estimated using Restricted Maximum Likelihood (REML) estimation with absolute diurnal cortisol and CRP levels as outcomes. These analyses were conducted through a stepwise model building approach. As multilevel models work by assuming that participants' data over time are correlated with each other, the first step was

then to specify the covariance structure. Two plausible structures, i.e., heterogeneous first order autoregressive structure and unstructured covariance structure, were tested. To identify which structure provided the best model fit, models were compared using Aikaike's Information Criterion (AIC) and Schwartz's Bayesian Information Criteria (BIC) values.

Next, separate unconditional multilevel growth models were estimated to assess the optimal nature and shape of change in absolute diurnal cortisol and CRP levels over time (objective 1). This was done by including a *time* and *time* by *time* variable to model the linear and non-linear effect of time, respectively, as compared to a model without a time variable (i.e., a model assuming no change). Models assuming no change, linear change, and non-linear (quadratic) change were compared using AIC and BIC values. Second, to examine whether change in absolute diurnal cortisol levels predicted change in CRP levels (objective 2), a conditional multilevel growth model with CRP as the outcome variable and absolute diurnal cortisol as unique Level-1 predictor was estimated. Given that Level-1 predictors can contain both intra- and inter-individual variability, grand-mean and group-mean (also called person-mean) centered values were computed for absolute diurnal cortisol levels to allow for the disaggregation of intra- and inter-individual effects of absolute diurnal cortisol on CRP levels (Bauer and Curran, 2016; Curran and Bauer, 2011). No other predictor was included in this model. Finally, in order to assess if behavioural, physical, and psychological variables predict absolute diurnal cortisol and CRP levels (objective 3), a seperate model for each candidate predictor (i.e., ST, MVPA, BMI, depressive symptoms, perceived general stress, and cancer-related stress) was estimated, for a total of 12 models (six with absolute diurnal cortisol levels as the outcome variable and six with CRP levels as the outcome variable). All predictors were time-varying and therefore included as Level-1 variables. Additionally, each Level-1 predictor was decomposed by calculating grand-mean and group-mean centered variables (Curran and Bauer, 2011). Because it was assumed that not all participants had the same levels at T1 or rate of change over time, models with fixed effects only and models with both fixed and random effects were tested and compared. General conclusions remained unchanged when candidate predictors were allowed to vary across persons (i.e., when random effects were included) and when they were not (i.e., when only fixed effects were included). However, including random effects led to worse model fit, and the variance around the slopes were not significant, suggesting the rate of change was not different across persons. They were therefore excluded from the analyses. The retained conditional multilevel growth model for each candidate predictor was re-tested with potential confounding variables available within the database measured at T1 (i.e., age, education, cancer stage, medication use, time since diagnosis, hormonal treatment, smoking status). The general conclusions drawn from the adjusted models did not differ from the unadjusted models; therefore, only results from the unadjusted models are presented for parsimony.

3. Results

3.1. Participants characteristics

Socio-demographic and cancer-related characteristics for the analytical samples (cortisol, $n = 192$; CRP, $n = 168$) are depicted in Table 1. Participants were, on average, 55 years old, self-identified as White (> 85%), were post-menopausal (> 64%), and married or living with a spouse (> 63%). Most of them were diagnosed with stage I or II breast cancer (> 81%) and received chemotherapy as part of their treatment regiment (> 64%).

3.2. Summary of main results

Overall, results indicated that absolute diurnal cortisol levels did not significantly change over time post-treatment, but that CRP levels significantly decreased over time, albeit in a non-linear fashion and these changes were not predicted by initial levels and changes in absolute diurnal cortisol levels. In the prediction of absolute diurnal cortisol levels, increases in participants' ST level (relative to their own average levels) were associated with a reduction of absolute diurnal cortisol levels (intra-individual level association), while having higher overall ST (relative to others) was associated with higher overall absolute diurnal cortisol levels (inter-individual level association). In addition, engaging in more PA, having a lower BMI, and reporting lower health- and cancer-related stress (relative to others) was associated with lower overall CRP levels (inter-individual level associations).

Table 1
Characteristics of participants included in the analyses.

Demographic characteristics	Cortisol ($n = 192$)	C-reactive protein ($n = 168$)
Age [mean years [SD] (range)]	55.1 [11.0] (28.0–79.0)	55.2 [11.0] (28.0–79.0)
Ethnicity [*n* White (%)]	163 (84.9)	144 (85.7)
Relationship status [*n* (%)]		
Single, divorced/separated, or widowed	68 (35.4)	61 (36.4)
Married or living with a life partner	124 (64.6)	107 (63.7)
Highest level of education attained [*n* (%)]		
College, technical degree or below	95 (49.5)	81 (48.2)
University undergraduate degree or above	97 (50.5)	87 (51.8)
Household income ($CAD) [median]	70,000	70,000
Time since diagnosis [mean months [SD] (range)]	10.6 [3.4] (2.0–20.0)	10.5 [3.5] (2.0–20.0)
Received chemotherapy [*n* (%)]	123 (64.1)	109 (64.9)
Post-menopausal [*n* (%)]	126 (65.6)	109 (64.9)
Cancer stage [*n* (%)]		
I	79 (41.4)	67 (39.9)
II	76 (39.6)	70 (41.7)
III	37 (19.3)	31 (18.5)
Predictors [grand mean [SD] (range)]		
Weekly sedentary time (min)	4215.8 [680.4] (1984.8–6096.0)	4312.8 [690.9] (1984.8–6096.0)
Weekly MVPA time (min)	103.0 [81.9] (0.0–526.0)	102.7 [80.5] (0.0–459.3)
Body mass index	26.0 [5.3] (17.4–50.2)	26.3 [5.4] (17.4–50.1)
Depressive symptoms	1.7 [0.5] (1.0–3.7)	1.7 [0.5] (1.0–3.7)
General stress	2.5 [0.6] (1.0–4.6)	2.6 [0.6] (1.0–4.2)
Health- and cancer-related stress	2.5 [0.8] (1.0–4.0)	2.6 [0.8] (1.0–4.0)

Note. *MVPA* = moderate-to-vigorous intensity physical activity.

3.3. Objective 1: how do absolute diurnal cortisol and CRP levels change over time post-treatment?

A heterogeneous first order autoregressive structure minimized AIC and BIC values and was therefore retained both for cortisol and CRP levels models. This structure assumes homogeneous variances and correlations that decline exponentially with distance. In this case, this means that the variability in a measurement (e.g., cortisol) is constant regardless of which time point it was measured at. It also means that two measurements that are adjacent in time are most highly correlated and that as measurements get further and further apart, they are less and less correlated. Using a heterogeneous first order autoregressive structure, a model assuming no change over time was retained for absolute diurnal cortisol levels based on AIC and BIC values. In this retained model, the fixed estimate indicated that there was a significant mean intercept ($B = 10.90$, standard error [SE] $= 0.12$, $p < .01$), indicating that the average level of absolute diurnal cortisol was significantly different from zero; however, the model implied that levels remain stable over time ($B_{linear} = 0.05$, SE $= 0.04$, $p = .17$). For CRP, a model assuming non-linear (i.e., quadratic) change was retained. In this retained model, the fixed

estimates indicated that there was a significant mean intercept ($B = 1.45$, SE = 0.14, $p < .01$), indicating that the average level of CRP was significantly different from zero. It also implied that CRP levels changed over time in a curvilinear way, whereby levels decreased over time but more sharply initially ($B_{linear} = -0.31$, SE = 0.11, $p = .01$; $B_{quadratic} = 0.05$, SE = 0.02, $p = .03$). Table 2 provides scores for absolute diurnal cortisol and CRP levels over the five time points.

3.4. Objective 2: is change in CRP levels predicted by initial levels or change in absolute diurnal cortisol levels?

Results indicated no statistically significant association between absolute diurnal cortisol and CRP levels both at the inter- ($B = 0.07$, SE = 0.05, $p = .15$) and intra-individual level ($B = -0.05$, SE = 0.06, $p = .39$). This means that differences in levels of absolute diurnal cortisol *between* participants' did not account for the changes in CRP levels over time, and that differences *within* participants' levels of absolute diurnal cortisol over time did not explain the decreases in CRP levels, respectively.

3.5. Objective 3: what variables predict absolute diurnal cortisol and CRP levels?

The results of the conditional multilevel growth models are presented in Table 3. When comparing the conditional multilevel growth models with the unconditional multilevel models, the conditional multilevel models with statistically significant predictors resulted in a reduction in AIC and BIC values, indicating better fit. This implies that the addition of these predictors helped to explain significant individual differences in absolute diurnal cortisol and CRP levels.

3.5.1. Predicting absolute diurnal cortisol levels

Results showed that ST, both at the inter- ($B < 0.01$, SE < 0.01, $p = .01$) and intra-individual level ($B = -0.01$, SE = 0.01, $p < .01$), was significantly associated with absolute diurnal cortisol levels. The significant inter-individual level association indicates that participants who generally reported higher ST (as compared to others) had overall higher levels of absolute diurnal cortisol. The significant intra-individual level association, on the other hand, indicates that participants had lower absolute diurnal cortisol levels when they engaged in more ST (as compared to their own average across time points). MVPA, BMI, depressive symptoms and perceived general and health- and cancer-related stress were not significantly associated with absolute diurnal cortisol levels, either at the inter- or intra-individual levels (*Bs* ≤ 0.24, SEs ≥ 0.33, *ps* ≥ .18).

3.5.2. Predicting CRP levels

Results indicated an inter-individual level association between CRP levels and MVPA ($B = -0.004$, SE < 0.01, $p < .01$), BMI ($B = 0.10$, SE = 0.01, $p < .01$), and health- and cancer-related stress ($B = 0.240$, SE = 0.12, $p = .04$). These results mean that participants who generally engaged in more MVPA, had a lower BMI, and reported lower health- and cancer-related stress (as compared to others), had overall lower CRP levels. There was no intra-individual level association between CRP levels and MVPA, BMI, and health- and cancer-related stress. Similarly, there was no inter- and intra-individual level associations between CRP levels and ST, depressive symptoms, and perceived general stress (*Bs* ≤ 0.20, SE s≥ 0.24, *ps* ≥ .14).

Table 2
Means and standard deviations of cortisol and CRP levels over the five time points.[a].

Time point	Cortisol (nmol/Lxh)	C-reactive protein (mg/L)
T1: 3.5 months post-treatment [mean [SD] (range)]	10.78 [1.78] (7–16)	1.43 [1.67] (0–8)
T2: 6.5 months post-treatment [mean [SD] (range)]	11.27 [2.47] (5–18)	1.21 [1.38] (0–8)
T3: 9.5 months post-treatment [mean [SD] (range)]	11.07 [2.14] (6–16)	1.08 [1.28] (0–9)
T4: 12.5 months post-treatment [mean [SD] (range)]	10.55 [2.12] (5–15)	1.13 [1.35] (0–9)
T5: 15.5 months post-treatment [mean [SD] (range)]	11.29 [2.25] (5–18)	1.16 [1.61] (0–10)

[a] Values are different than the ones reported in Lambert et al. (2020) given the larger sample of the current study.

Table 3
Fixed effect results of multilevel modeling analyses testing time-varying predictors of absolute diurnal cortisol and CRP levels in BCS.

	Absolute diurnal cortisol levels			CRP levels		
	B	SEs	*ps*	*B*	SEs	*ps*
Sedentary time						
Intercept	10.881	0.118	<.01*	1.457	0.142	< .01*
Time	–	–	–	−0.316	0.115	< .01*
Time squared	–	–	–	0.056	0.025	.03*
Inter-individual effect	<0.001	<0.001	.01*	<0.001	<0.001	.62
Intra-individual effect	−0.001	<0.001	<.01*	−0.001	<0.001	.81
MVPA						
Intercept	10.875	0.119	<.01*	1.455	0.139	< .01*
Time	–	–	–	−0.302	0.114	< .01*
Time squared	–	–	–	0.051	0.025	.04*
Inter-individual effect	0.001	0.002	.41	−0.004	0.001	< .01*
Intra-individual effect	−0.002	0.002	.42	0.002	0.001	.14
Body mass index						
Intercept	10.845	0.119	<.01*	1.406	0.139	< .01*
Time	–	–	–	−0.303	0.117	.01*
Time squared	–	–	–	0.055	0.026	.03*
Inter-individual effect	0.010	0.022	.67	0.096	0.014	< .01*
Intra-individual effect	0.091	0.068	.18	−0.049	0.043	.26
Depressive symptoms						
Intercept	10.863	0.120	<.01*	1.451	0.142	< .01*
Time	–	–	–	−0.300	0.115	.01*
Time squared	–	–	–	0.0527	0.025	.04*
Inter-individual effect	0.240	0.277	.39	0.195	0.202	.34
Intra-individual effect	−0.360	0.331	.28	−0.146	0.239	.54
Perceived general stress						
Intercept	10.850	0.120	<.01*	1.455	0.143	< .01*
Time	–	–	–	−0.313	0.116	.01*
Time squared	–	–	–	0.0548	0.025	.03*
Inter-individual effect	0.189	0.120	.47	−0.067	0.189	.72
Intra-individual effect	−0.273	0.316	.39	0.195	0.222	.38
Health- and cancer-related stress						
Intercept	10.883	0.120	<.01*	1.460	0.141	< .01*
Time	–	–	–	−0.304	0.115	.01*
Time squared	–	–	–	0.053	0.025	.04*
Inter-individual effect	−0.206	0.167	.22	0.240	0.118	.04*
Intra-individual effect	0.127	0.208	.54	−0.120	0.152	.43

Notes. MVPA = moderate-to-vigorous intensity physical activity. *B* = estimate; *SE* = standard error. Separate models were tested for each variable to conserve statistical power. Parameters are unstandardized coefficients.
*$p < .05$.

4. Discussion

The objectives of this study were to (1) describe BCS' absolute diurnal cortisol and CRP level patterns over the first 1.5 year post-treatment, (2) assess whether change in CRP levels was predicted by initial levels and/or rate of change in absolute diurnal cortisol levels, and (3) present the associations between absolute diurnal cortisol and CRP levels and a wide range of modifiable behavioural, physical, and psychological variables. ST, depressive symptoms, perceived general stress, and health- and cancer-related stress were considered as candidate predictors of absolute diurnal cortisol and CRP levels. Based on previously published findings by our team (Lambert et al., 2020; Sabiston et al., 2018a), MVPA and BMI were also included to take their variance into consideration in our models. Results indicated that absolute diurnal cortisol levels did not significantly change over time post-treatment, but that CRP levels significantly decreased over time, albeit in a non-linear fashion and these were not predicted by initial levels and change in absolute diurnal cortisol levels. In the prediction of absolute diurnal cortisol levels, increases in participants' ST (relative to their own average) were associated with a reduction of absolute diurnal cortisol levels (intra-individual level association), while having higher overall ST (relative to others) was associated with higher overall absolute diurnal cortisol levels (inter-individual association). In addition, engaging in more PA, having a lower BMI, and reporting lower health- and cancer-related stress (relative to others) was associated with lower overall CRP levels (inter-individual level associations).

Very few studies have assessed the nature and shape of change in absolute diurnal cortisol and CRP levels over time in cancer survivors post-treatment. Hsiao et al. (2017) found that diurnal cortisol levels fluctuated over time post-treatment in BCS, whereby diurnal patterns changed from a flatter to a steeper slope, suggesting a trend towards recovery. These changes were not observed in this study. Indeed, in contrast to the hypothesis, absolute diurnal cortisol levels did not significantly fluctuate from approximately 3.5 to 15.5 months post-treatment. Given that some studies observed no diurnal cortisol level dysregulation post-treatment in BCS when compared to women with no history of cancer (Couture-Lalande et al., 2014; Zeitzer et al., 2016), it is possible that participants in this study also did not exhibit cortisol dysregulation in the first place, thus explaining the absence of return-to-recovery evidence. Villasenor et al. (2014) reported that CRP levels decreased over time in BCS. Consistent with these findings, the results support this trend and provide further insight into the nature of change from treatment completion onwards. Whilst Villasenor et al. (2014) showed that CRP levels return to normal ranges following cancer treatment, they could not assess whether levels changed in a linear or non-linear fashion due to the design of their study. In this study, with five assessments spanning a 15.5-month period, results show that CRP levels decreased in a non-linear, quadratic pattern. CRP levels have been identified as a very sensitive marker of tumour growth and metastasis (Mantovani et al., 2008; Seruga et al., 2008; Villasenor et al., 2014). The rapid initial decrease in CRP levels observed post-treatment completion could thus imply that the cessation of treatment coincided with tumour deletion. Additionally, treatment completion also typically corresponds to a time when BCS return to usual activities and experience improvements in quality of life, vitality, and treatment-related stress (Connerty and Knott, 2013; Costanzo et al., 2007), all of which could contribute to the rapid initial decrease in CRP levels. The slow-down in decrease over time can be explained by factors such as stress with regard to going back to work and expectations to return to previous roles and responsibilities, fatigue, as well as hormonal disruption following treatment (Allen et al., 2008; Bower et al., 2007). Further research is needed to gain a better understanding of the underlying mechanisms and factors involved in cortisol and CRP level fluctuations post-treatment for breast cancer.

No evidence of intra- or inter-individual level associations between absolute diurnal cortisol and CRP levels was found in this study. Chronic exposure to elevated levels of cortisol (as it might be the case in situation of long-term stress such as an experience of cancer) may weaken the sensitivity of immune cell receptors and make them non-responsive to cortisol-mediated signaling, thereby interfering with the transduction of the typical physiological effects of cortisol on CRP and immune functions (Miller et al., 2008; Rueggeberg et al., 2012). Additional research is needed to gain further insight into the cortisol-CRP relationship reported in other studies and examine whether other variables may influence the relationship (Sharpley et al., 2019).

It is widely known that high ST is associated with important health risks, both physical and psychological (Allen et al., 2019; Biswas et al., 2015; Zhai et al., 2015). In BCS, highST has been associated with a higher incidence of comorbid conditions, greater fatigue and pain severity, depression, and lower health-related quality of life (George et al., 2013; Phillips et al., 2016; Trinh et al., 2015). Studies investigating the association between ST and cortisol levels have found mixed results (Nabi et al., 2016; Jackson et al., 2019; Teychenne et al., 2018). In this study, participants who reported higher ST (relative to others) had higher absolute diurnal cortisol levels (i.e., inter-individual level association). This finding could be partly explained by the fact that sedentary individuals typically report greater fatigue, lower energy levels, and poorer mental health than active individuals (Ellingson et al., 2014; Sanchez-Villegas et al., 2008). In turn, fatigue and mental health difficulties (e.g., depression) have been associated with increased cortisol levels in BCS (Hsiao et al., 2012; Schmidt et al., 2016). In addition, results of this study show that fluctuations in ST within participants is associated with absolute diurnal cortisol levels. Specifically, results suggest that increases in participants' ST (as compared to their own average) was associated with lower absolute diurnal cortisol levels (i.e., intra-individual level association). Whilst this intra-individual level association is in the opposite direction than the inter-individual association, it supports the notion that observing an inter-individual level association does not guarantee a similar intra-individual level association and vice versa (Hox, 2010), and underscores the value of using analytical approaches that can consider both intra- and inter-individual level associations (e.g., MLM). To explain the inverse association, researchers may want to consider the type of ST activity. It is possible that participants may have engaged in lower-arousal ST activities (such as reading and napping vs. higher-arousal ST activities such as watching a scary movie and playing video games) on those particular days. However, data on type of ST activity were not collected. Considering that BCS spend most of their waking hours engaging in ST and generally have higher ST than individuals without a history of cancer (Kim et al., 2013; Sweegers et al., 2019), it is imperative to establish whether ST plays a role in the physiological outcomes of BCS post-treatment, and if so, which type of ST activities. Moreover, based on the inter-individual results in this study, interventions targeting BCS with high ST levels could be an effective strategy to promote optimal health outcomes in BCS. Additional studies to confirm these associations are however warranted.

Lower MVPA, higher BMI, and greater health- and cancer-related stress were associated with higher CRP levels in general based on observed inter-individual level associations. Together, these variables are known to contribute to poorer general health outcomes, including increased morbidity and all-cause mortality (Bauman et al., 2017; Strohacker et al., 2013), thereby providing an explanation for their associations with elevated CRP levels. These findings are in line with several studies conducted in the general population (Colbert et al., 2004; Costa et al., 2019; Timpson et al., 2011) as well as in BCS (Asegaonkar et al., 2015; Babaei et al., 2015). They also confirm inter-individual level associations observed by our team between CRP levels, MVPA and BMI using conventional analyses (Lambert et al., 2020), and thus echo ours and others previous recommendations to implement of weight management and PA interventions to decrease inflammatory levels and promote optimal health post-treatment among BCS (Ballard-Barbash et al., 2012; Fairey et al., 2005; Sabiston et al., 2018a). In addition though, the inter-individual level associations between health- and cancer-related stress and CRP levels underline that other factors, not previously

examined, may help to explain why some BCS report more physiological dysregulation than others – i.e., those with higher stress levels. These novel results suggest that lowering health- and cancer-related stress in BCS may further help to enhance BCS' health post-treatment. Indeed, they add that helping BCS effectively manage stress may improve the efficacy of weight management and PA interventions.

Depressive symptoms and perceived general stress were not associated with absolute diurnal cortisol and CRP levels in this sample of BCS. These findings are dissimilar to those of McFarland et al. (2018) and Ricci et al. (2018) who found positive associations between these psychological variables and CRP levels in cancer survivors. Speculatively, the lack of association in this study may be explained by participants' relatively low reporting of depressive symptoms and general stress, as well as the limited variability in those variables. Alternatively, it may be explained by the timing of the assessments in this study. Some have suggested that depressive symptoms and stress experienced by cancer survivors might be *outcomes* of inflammatory pathway activation rather than *predictors* (Lee et al., 2004; Miller et al., 2008). Accordingly, CRP levels during treatment could predict later depressive symptoms and stress post-treatment (T1−T5). Additional longitudinal studies covering both treatment and post-treatment phases with larger samples reporting varying levels of depressive symptoms and stress are warranted to further assess the nature, timing, and direction of these relationships. Nevertheless, continued monitoring, prevention and treatment of depressive symptoms and stress remains of crucial clinical relevance given their high prevalence in BCS (Badger et al., 2004; Groarke et al., 2013; Stanton, 2006) and because these psychological states may impair PA/ST behaviour post-treatment (Spector et al., 2013; Ventura et al., 2013), which was found to be predictors of cortisol and CRP levels in this study.

4.1. Strengths & limitations

The repeated measurement of a wide range of behavioural, physical, and psychological predictors in BCS constitutes an important contribution to the cancer survivorship literature. The inclusion of six distinct modifiable candidate predictors into our models allows for a powerful approach to gaining of greater understanding of the influence of general lifestyle habits and psychological health on outcomes in cancer survivors. Very few studies have included such frequent data collections and focused on the early post-treatment phase of cancer survivorship and the current study addresses this gap in the literature (Allen et al., 2008; Roundtree et al., 2011; Stanton, 2012). Extending from the results from our previous work (Lambert et al., 2020; Sabiston et al., 2018a), the analytical techniques employed overcome some of the limitations in the current literature by examining both intra- (within) and inter- (between) individual level associations and trends. The objective and precise assessment of both ST and PA, as well as the relatively large sample size, are other strengths of the study. Nonetheless, this study also has limitations. First, although self-report is appropriate to assess depressive symptoms and different types of perceived stress (Gotay and Pagano, 2007; Roberti et al., 2006; Vodermaier et al., 2014), some bias may have affected the results (due to socially desirable responding, for instance). A second limitation is that participants volunteered to take part in this study, with the majority of them being White, on average 55 years of age, post-menopausal, well-educated, and diagnosed with early-stage breast cancer, thereby limiting the ability to generalize the findings to all BCS. Finally, this study is non-experimental and therefore inferences of causality and direction of effects cannot be made.

5. Conclusion

Given that cancer survivors with persistent post-treatment physiological dysregulations have elevated risk of adverse health outcomes (Reza et al., 2014; Schrepf et al., 2013; Sharpley et al., 2019), studies aiming to identify cancer survivors at greater risk of such dysregulations are of high priority. This study provides evidence that lifestyle modification interventions (including weight management, stress reduction, and activity level strategies) might be effective, non-pharmaceutical strategies to promote physiological health in BCS. Data on ST and PA parameters such as frequency (e.g., everyday for shorter periods of time vs. only twice a week but for longer periods of time), intensity (e.g., high intensity interval training vs. moderate intensity continuous exercise), type (e.g., strength training vs. aerobic training; video games vs. watching television vs. reading), context (e.g., indoors vs. outdoors or individual vs. group-based), and time of the day should be collected in future studies to enable the development of the most optimal and beneficial interventions.

Declaration of competing interest

All authors certify no potential conflict of interest to disclose.

Acknowledgement

We gratefully acknowledge the women who participated in this study, without whom our research could not be conducted. This research was supported by a Canadian Institutes of Health Research grant (Grant no. 123358).

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