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Longitudinal associations between inflammatory markers and fatigue up to two years after colorectal cancer treatment

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LONGITUDINAL ASSOCIATIONS BETWEEN INFLAMMATORY MARKERS AND FATIGUE UP TO TWO YEARS AFTER COLORECTAL CANCER TREATMENT

Nadira R. Querido[1], Marlou-Floor Kenkhuis[1], Eline H. van Roekel[1], Stéphanie O. Breukink[2,3,4], Fränzel J.B. van Duijnhoven[5], Maryska L.G. Janssen-Heijnen[1,6], Eric T.P. Keulen[7], Per Magne Ueland[8], F. Jeroen Vogelaar[1], Evertine Wesselink[5], Martijn J.L. Bours[1], Matty P. Weijenberg[1]

1 Department of Epidemiology, GROW School for Oncology and Reproduction, Maastricht University, Maastricht, the Netherlands

2 Department of Surgery, Maastricht University Medical Centre+, Maastricht, the Netherlands

3 GROW School for Oncology and Reproduction, Maastricht University Medical Centre+, Maastricht, the Netherlands

4 NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Centre+, Maastricht, the Netherlands

5 Division of Human Nutrition and Health, Wageningen University & Research, Wageningen, the Netherlands

6 Department of Clinical Epidemiology, Viecuri Medical Center, Venlo, the Netherlands

7 Department of Internal Medicine and Gastroenterology, Zuyderland Medical Centre, Sittard-Geleen, the Netherlands

8 BEVITAL, 5021 Bergen, Norway

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Corresponding author: Matty P. Weijenberg, Maastricht University, Department of Epidemiology, GROW School for Oncology and Reproduction, P.O. BOX 616, 6200 MD Maastricht, the Netherlands. Phone: +31 43 3882393 E-mail: mp.weijenberg@maastrichtuniversity.nl

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Abstract

Background: Fatigue is often reported by colorectal cancer survivors (CRC) and largely impacts their quality of life. Inflammation has been linked to fatigue mainly in breast cancer patients. Therefore, we investigated how inflammation is longitudinally associated with fatigue in CRC survivors, up to 2 years post-treatment.

Methods: A total of 257 patients from the ongoing Energy for life after ColoRectal cancer (EnCoRe) cohort study were included in the analysis. Plasma levels of IL6, IL8, IL10, TNFα, hsCRP, and fatigue were measured at 6 weeks, 6, 12, and 24 months post-treatment. Fatigue was measured through the validated Checklist Individual Strength (CIS total, 20-140), consisting of four subscales – subjective fatigue (8-56), motivation (4-28), physical activity (3-21), and concentration (5-35), and the EORTC QLQ-C30 fatigue subscale (0-100). Linear mixed-models were used to assess the confounder-adjusted longitudinal associations between inflammatory markers and overall fatigue along with the subscales.

Results: Mean levels of CIS fatigue decreased from 62.9 at 6 weeks to 53.0 at 24 months. In general, levels of inflammatory markers also decreased over time. No statistically significant longitudinal associations were found between IL6, IL8, IL10, TNFα, and fatigue. Higher levels of hsCRP were associated with more CIS fatigue (β per SD 3.21, 95% CI 1.42; 5.01) and EORTC fatigue (β 2.41, 95% CI 0.72; 4.10).

Conclusion: Increased levels of hsCRP are longitudinally associated with more post-treatment fatigue in CRC survivors.

Impact: These findings suggest that low-grade inflammation may play a role in fatigue reported by CRC survivors up to 2 years post-treatment.

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1. Introduction

Population ageing, screening programs, early detection, and more effective treatments have led to an increase in the number of colorectal cancer (CRC) survivors (1). In 2020, worldwide, over 5 million individuals had a CRC diagnosis in the past 5 years (2). Due to the rising number of CRC survivors, it becomes increasingly important to address factors that impact their health-related quality of life (HRQoL) post-treatment. There are several chronic or late effects caused by both CRC and its treatment, such as fatigue, pain, bowel dysfunction, and emotional distress, all of which can affect a patient's HRQoL (3, 4).

Fatigue is a common and debilitating symptom experienced by CRC survivors during and post-treatment (5, 6). Reported rates of fatigue among CRC survivors range from 12-69.7% depending on the measurement instrument used and time elapsed since treatment (6-10). Results from prospective studies, including ours, and a systematic review showed that fatigue peaked between 6 weeks and 6 months post-treatment but persisted up to two years post-treatment (9, 11, 12). Many factors, such as treatment, comorbidities, and physical and psychological factors, possibly contribute to cancer-related fatigue (5, 13). Furthermore, there is an increasing interest in the underlying biological mechanisms of fatigue (14).

Inflammation has been mainly identified as an underlying mechanism in post-treatment cancer-related fatigue, with the majority of studies performed in breast cancer survivors (13, 15, 16). Current thought is that production of proinflammatory cytokines in the periphery stimulates the brain resulting in fatigue, among other sickness behaviors (17, 18). Indeed, elevated circulating levels of pro-inflammatory markers, such as interleukin (IL)-6, tumor necrosis factor-α (TNFα) and C-reactive protein (CRP), have been linked to more fatigue in breast cancer survivors (15, 19, 20). In contrast, anti-inflammatory cytokines, such as IL10, may attenuate sickness behavior, but little is known in relation to cancer-related fatigue (18,

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21). Most longitudinal studies exploring the association between cancer-related fatigue and inflammation in breast cancer survivors focus on the period during or up to 6 months post-treatment and therefore have not assessed longer term effects (22, 23). In addition, there are important differences between breast cancer and CRC survivors regarding several characteristics, namely age, sex, and treatment, that can differentially affect fatigue. Some studies point to sex differences in both immune response and reporting of fatigue (24-27). Thus, despite the evidence of links between inflammation and fatigue in breast cancer survivors, a further exploration of this association is needed in CRC survivors.

Few studies, with differing methodologies, have explored the link between inflammation and fatigue in CRC survivors (9, 28-30). These methodological differences include the measurement instruments used to assess fatigue, the start (pre- or post-treatment) and duration of follow-up time, and the availability of repeated measurements for both the inflammatory markers and fatigue. To our knowledge, only one study investigated the association between several inflammatory markers, excluding hsCRP, and fatigue up to two years post-treatment with repeated measurements over time (9).

Investigating how post-treatment inflammation is related to post-treatment fatigue over time will help to better understand the role of inflammation in the progression of cancer-related fatigue in CRC survivors. Therefore, the primary aim of this study is to determine how plasma levels of inflammatory markers, namely IL6, IL8, IL10, TNFα, high-sensitivity C-reactive protein (hsCRP), are longitudinally associated with overall fatigue, as well as different dimensions of fatigue (subjective fatigue, motivation, physical activity, and concentration) in CRC survivors followed up from 6 weeks until 2 years post-treatment.

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2. Methods

2.1. *Study design and population*

Data analysis was performed with longitudinal data collected from April 18th, 2012 up until November 1st, 2016, from the Energy for life after ColoRectal cancer (EnCoRe) study. The EnCoRe study is an ongoing prospective cohort study with patient recruitment at three participating centers: Maastricht University Medical Center+, VieCuri Medical Center, and Zuyderland Medical Centre (31). Eligible for participation were men and women above the age of 18, diagnosed with stage I-III CRC. Exclusion criteria were stage IV CRC, inability to understand and speak Dutch, residential address outside of the Netherlands, or the presence of comorbidities that could impede a successful study participation, including cognitive and visibility/hearing disorders (31).

Patients were enrolled at diagnosis and followed up with repeated measurements at 6 weeks (n=237), 6 months (n=184), 12 months (n=150), and 24 months post-treatment (n=63) Study measurements were performed during home visits. In case participants were ill (e.g. the flu) or hospitalized, home visits were postponed. Participation rate at diagnosis was 46% and >90% at all post-treatment follow-up visits (Supplemental Figure 1). The main reason for the decrease in sample size as follow-up time increases was that not all participants included at diagnosis had reached the subsequent follow-up points on November 1st, 2016. The EnCoRe study was approved by the Medical Ethics Committee of the Academic Hospital Maastricht and Maastricht University, the Netherlands (Netherlands Trial Register no. NL6904). The study was conducted in accordance with the principles of the Declaration of Helsinki (version 7, October 2008).

2.1. *Plasma inflammatory markers (exposure)*

Fasting blood samples collected during home visits at 6 weeks, 6, 12, and 24 months post-treatment were used to assess plasma levels of inflammatory markers. After collection into

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EDTA tubes, blood samples were centrifuged, aliquoted into plasma, and stored in a freezer at -80^{o}C until analysis (32). A custom-made multiplex assay using electrochemiluminescence detection (Meso Scale Diagnostics, Rockville, MD, USA) was used to measure plasma concentration (pg/ml) of IL6, IL8, IL10, and TNFα. Assay plates were analysed on a QuickPlex SQ 120 plate reader (Meso Scale Diagnostics), according to manufacturer's instructions, at Wageningen University & Research, as described previously (32). Alongside the calibration curve, three quality controls were included per plate. All samples were analysed in duplicates and the sample mean was accepted if the coefficient of variation (CV) was <40% (32). Inter- and intra-assay CVs were <8%, with reported values deviating less than 15% from target values (32). Levels of hsCRP were measured at 6 weeks, 6 and 12 months post-treatment. Plasma concentration (μg/ml) of hsCRP was determined through an immuno-MALDI (matrix-assisted laser desorption/ionization) mass spectrometry method (BEVITAL, Bergen, Norway) (33). The inter-assay CV ranged from 3-6%. hsCRP is used to measure lower levels of CRP which reflect low-grade systemic inflammation (34, 35).

Summary inflammatory z-scores were calculated to group the inflammatory markers and improve statistical efficiency (32, 36). Higher z-scores indicate higher levels of inflammation. First, normalized z-scores from each inflammatory marker were calculated as $z = (x_{ij} - \mu_j) / \sigma_j$, in which x is the participant's (i) inflammatory marker value at a given visit (j), μ is the study population mean, and σ is the study standard deviation, both at given visits (j) (32). Two summary inflammatory z-scores were computed for each participant, at each time point, to use all available data. One was calculated by summing the normalized z-scores of IL6, IL8, TNFα, hsCRP, and subtracting IL10, and thus only includes patients with measurements up to 12 months post-treatment. The other summary inflammatory z-score excluded hsCRP thereby including patients with data available at all post-treatment time points.

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2.2. *Fatigue (outcome)*

The validated Checklist Individual Strength (CIS) and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) fatigue subscale were used to measure fatigue at 6 weeks, 6, 12, and 24 months post-treatment. The CIS is a 20-item questionnaire composed of 4 subscales – subjective fatigue (8-56), motivation (4-28), physical activity (3-21), and concentration (5-35) (37). The total fatigue score (20-140) was obtained by summing all item scores. Higher scores represent higher levels of fatigue. The EORTC QLQ-C30 fatigue subscale contains 3 items and ranges from 0-100 (38).

Although initially developed for patients with chronic fatigue syndrome (37), the CIS has been used to measure fatigue in cancer survivors (39). In a study among working people, the CIS was able to adequately distinguish fatigued and non-fatigued individuals (40). A recent study assessed the construct validity of the CIS subjective fatigue subscale and the EORTC QLQ-C30 fatigue subscale in cancer survivors (n=320) and found a high Spearman rank correlation coefficient of 0.77 (41).

2.3. *Other relevant variables*

At the time of diagnosis, patients reported sex and birth date, which was used to calculate the age at each post-treatment time point (11). Data on treatment, such as chemotherapy and radiotherapy, were obtained from clinical records. The number of comorbidities at each post-treatment time point was determined using the 13-item Self-Administered Comorbidity Questionnaire (42). Height and weight, measured by trained dietitians, were used to calculate body mass index (BMI) at every time point. Current smoking status at each time point was self-reported. Information on use of non-steroidal anti-inflammatory drugs (NSAIDs) during the 6 months prior to the follow-up time point was collected using self-reported questionnaires (32). Physical activity was evaluated using the

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validated Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH) (43). Ainsworth's Compendium of Physical Activities was used to give activities a metabolic equivalent of task (MET) value (44). Activities were categorized as light-physical activity (LPA) (<3 MET) or moderate-to-vigorous physical activity (MVPA) (≥3 MET), and total time spent in each activity was calculated as hours/week (11).

2.4. *Statistical analysis*

Descriptive analyses were performed to describe patient characteristics at 6 weeks (i.e. the baseline for longitudinal analyses). Categorical variables were presented as frequencies with percentages, and continuous variables as the mean with standard deviation (SD) or medians with interquartile range (IQR) for normally and non-normally distributed data, respectively. Data on inflammatory markers, summary inflammatory z-scores, and fatigue, including the subscales, were presented for all post-treatment time points.

Linear mixed model regression was used to investigate the longitudinal associations between levels of inflammatory markers and fatigue (45). The regression coefficients obtained are a weighted average of the inter-individual (between-subject) differences and intra-individual (within-subject) changes (45). Therefore, separate hybrid models were used to disentangle the intra- and inter-individual components (46). To estimate the intra-individual association, the deviation of an individual's level of inflammatory marker from the person-mean was modelled. The regression coefficient from this model represents changes in fatigue over time in relation to a one-unit change in levels of inflammatory markers over time within individuals. To estimate the inter-individual association, a centered person-mean value of an inflammatory marker – difference between a subject's mean value of the inflammatory marker and the sample mean – was modelled to obtain a regression coefficient which indicates the average difference over time in fatigue between individuals in relation to a one-unit difference in mean levels of inflammatory markers between individuals.

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To improve interpretability, levels of inflammatory markers were divided by their SD at 6 weeks to obtain regression coefficients that represented the difference in fatigue per SD increase of the inflammatory marker. The first model included age at measurement (years), sex (men/women), and time since diagnosis (days). The second model included additional potential confounders, selected *a priori* based on the available literature: NSAIDs (yes/no), BMI (kg/m^2), physical activity (LPA and MVPA - hours/week), comorbidities (0, 1, ≥2), treatment (chemotherapy/radiotherapy, yes/no), and smoking status (yes/no). The likelihood ratio test was used to evaluate whether including a random slope improved the model fit (45). The false discovery rate (FDR) method ($q<0.05$) was used to correct for multiple testing of the various exposures with the outcome (47). This was applied separately for each outcome (CIS: total fatigue, subjective fatigue, motivation, physical activity, concentration; EORTC fatigue). No correction was performed for the inflammatory z-scores since they are correlated with the inflammatory markers.

Post-hoc subgroup analyses were performed for sex to explore the longitudinal associations in men and women separately; testing for interaction was done by including a product-term for the inflammatory marker and sex in each model. Sensitivity analyses excluding participants with recurrence and participants who died were performed.

To further explore the role of hsCRP, linear mixed model regression was performed with hsCRP categorized to represent normal values (≤3mg/L), low-grade inflammation (3-10mg/L), and acute inflammation (>10mg/L) (35, 48).

Statistical analyses were conducted in STATA (version 15). P-values below 0.05 (two-sided) after correction for multiple testing were considered statistically significant.

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2.5. *Data availability*

Data analysed in the manuscript, code book, and analytic code will be made available upon request pending (e.g., application and approval, payment, other) to co-author Dr. Martijn Bours.

3. Results

3.1. *Participant characteristics*

Data on fatigue and IL6, IL8, IL10, and TNFα was available for 237 participants at 6 weeks, 184 at 6 months, 150 at 12 months, and 63 at 24 months post-treatment. Data on fatigue and hsCRP was available for 200 participants at 6 weeks, 148 at 6 months, and 114 at 12 months post-treatment. Participants were on average 67 years old, and the majority were men (68.8%) (Table 1). There were some differences between men and women, notably a higher percentage of women had two or more comorbidities compared to men (women: 68.9%; men: 47.9%). Women also reported higher median levels of LPA than men (women: 14.0 hours/week, IQR 7.0-24.5; men: 6.3 IQR 1.2-12.0), but men reported higher median levels of MVPA than women (men: 9.0 hours/week, IQR 3.5-16.3; women: 4.1 IQR 1.5-7.0). The percentage of men who received radiotherapy was higher than women (men: 30.7%, women: 18.9%) and more men were diagnosed with rectum cancer (men: 42.3%, women: 29.7%).

3.2. *Fatigue and inflammatory markers*

Total fatigue was highest at 6 weeks post-treatment (62.9, SD 26.5) and decreased over time, with the largest decrease occurring between 6 and 12 months post-treatment (Figure 1, Table 2). Across all time points, women reported higher levels of fatigue compared to men. This was also observed in the subjective fatigue subscale, reduced motivation, reduced concentration, being most pronounced for subjective fatigue (Table 2, Supplemental Figure 2). The CIS total fatigue and EORTC fatigue subscale were significantly correlated at all time

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points (range: 0.68-0.76). Median levels of IL6, IL10, and TNFα slightly decreased over the course of 24 months post-treatment, and for levels of hsCRP up to 12 months post-treatment, while IL8 increased between the 12 and 24 months time points (Figure 1, Table 2). Pearson correlation coefficients indicated weak to moderated correlations between the inflammatory markers at 6 weeks (range: -0.02 to 0.45), with similar ranges at following time points (Supplemental Figure 3).

3.3. *Longitudinal associations between inflammatory markers and fatigue*

The coefficients presented represent the change in fatigue score for one SD increase of the inflammatory markers (Figure 2, Table 3, Supplemental Figure 4). In the fully adjusted models after FDR correction, there were no statistically significant overall, intra- or inter-individual associations between IL6, IL8, IL10, TNFα, and CIS total fatigue, as well as the subscales. Similar results were observed in the analyses with IL6, IL8, IL10, TNFα and the EORTC fatigue subscale.

After fully adjusting the model and FDR correction, higher levels of hsCRP were longitudinally associated with more CIS total fatigue (β 3.21, 95% CI 1.42; 5.01), subjective fatigue (β 1.82, 95% CI 0.94; 2.70), reduced motivation (β 0.85, 95% CI 0.41; 1.29), and EORTC fatigue (β 2.41, 95% CI 0.72; 4.10). Applying hybrid models revealed a significant inter-individual association between hsCRP and CIS total fatigue (β 5.44, 95% CI 1.61; 9.27). Additionally, higher levels of hsCRP were longitudinally associated with higher scores, both between- and within-subjects, in the subjective fatigue and reduced motivation subscales. The sensitivity analyses indicate that associations were similar after excluding participants who had a recurrence or died (Supplemental Table 1).

Analyses with the summary inflammatory z-score including hsCRP indicated that more inflammation was associated with more CIS total fatigue (β 2.42, 95% CI 0.06; 4.79) and

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EORTC fatigue (β 4.49, 95% CI 1.97; 7.01). For CIS total fatigue, an inter-individual association was observed (β 6.71, 95% CI 2.43; 11.00) while the intra-individual association was small and non-significant (β 0.69, 95% CI -2.07; 3.45). In the analyses with EORTC fatigue, both the inter-individual (β 5.75, 95% CI 1.39; 10.12) and intra-individual (β 3.92, 95% CI 0.93; 6.91) associations were statistically significant. The summary inflammatory z-score excluding hsCRP was associated with more EORTC fatigue (β 2.29, 95% CI 0.34; 4.24) but not with CIS total fatigue (β 0.74, 95% CI -1.13; 2.60). To ensure the 24-month time point was not responsible for the different results between the inflammatory z-scores including and excluding hsCRP, extra analyses excluding the 24-month time point were performed for the inflammatory z-score excluding hsCRP. The results led to the same conclusions with similar effect sizes between the inflammatory score excluding hsCRP and fatigue in which all time points were considered.

Results from the exploratory analysis indicated that survivors with levels of hsCRP between 3-10mg/L, and levels >10mg/L experienced more fatigue compared to those with levels ≤3mg/L (Figure 3, Supplemental Table 2). In subgroup analysis, the statistically significant associations after FDR correction for the individual inflammatory markers were only observed in men (Supplemental Table 3). Additionally, only 5 out of 84 interaction terms were statistically significant.

4. Discussion

No statistically significant associations were found between IL6, IL8, IL10, TNFα and CIS and EORTC fatigue after FDR correction. Higher levels of hsCRP were longitudinally associated with more fatigue from 6 weeks to 12 months post-treatment. Statistically significant inter-individual associations were observed, indicating that CRC survivors with higher mean levels of hsCRP over time reported higher scores of total fatigue. Similar trends were observed

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in the subjective and reduced motivation subscales, where both inter- and intra-individual associations for hsCRP were statistically significant. Additionally, statistically significant associations were found between the summary inflammatory score including hsCRP and both CIS and EORTC fatigue. Together these findings suggest that higher levels of low-grade inflammation are associated with more fatigue in CRC survivors.

Findings from longitudinal CRC studies are scarce and inconsistent, the latter likely due to methodological differences in the timing and frequency of measurements for the inflammatory markers and fatigue, the duration of follow-up time, and the types of measurement instruments used to assess the inflammatory markers and fatigue (22, 23). A recent study of 236 stage I-IV CRC survivors did not find statistically significant associations between levels of IL6, IL8, TNFα, CRP measured pre-surgery, and fatigue measured pre-surgery and at 6 and 12 months post-surgery (30). However, unlike this study, only pre-operative inflammatory markers were used, and fatigue was only measured using the EORTC QLQ-C30 fatigue subscale, which mainly measures physical fatigue. A study in patients with localized CRC found weak correlations of IL6, IL8, and IL10 with fatigue at 6 (ρ -0.16 to -0.20) and 24 months (ρ -0.16 to -0.30) after treatment, but not with TNFα (9). From the inflammatory markers we investigated, excluding hsCRP which was not measured, only IL8 was longitudinally inversely associated with more fatigue. Another study on CRC (n=50) and esophageal cancer (n=53) patients found a significant association between IL6 and a component score of fatigue-centered symptom cluster, but not between IL6, IL10, and fatigue severity (29). In the latter study, fatigue was measured weekly for 13 weeks after treatment initiated and the inflammatory markers were measured pre-treatment, during the 5-6 weeks of treatment, and 1 month post-treatment. Since IL10 is considered to have anti-inflammatory properties, it was expected to be inversely associated with fatigue (49, 50). We observed an inverse association

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between patients, for both CIS and EORTC fatigue, but this was non-significant after FDR correction. Although evidence is still scarce and inconsistent, higher levels of pro-inflammatory markers seem to be associated with more fatigue in CRC survivors.

A cross-sectional study in 299 disease-free breast cancer survivors, at 4 years post-diagnosis on average, reported a significant association between levels of hsCRP and fatigue (20). Other inflammatory markers, such as IL6, were analyzed but no statistically significant associations were found. Similar results were found in a longitudinal study in breast (n=28) and prostate cancer (n=20) survivors during radiotherapy (51). Both studies argued that pro-inflammatory cytokines, such as IL6, are produced in low quantities and thus harder to detect, possibly explaining the lack of association, as seen in our study (20, 51).

No other studies have used summary inflammatory z-scores to assess the association between inflammatory markers and fatigue. In our study, a significant association was found between the inflammatory z-score excluding hsCRP and EORTC fatigue. This association was not observed in the analysis with CIS fatigue and this difference is possibly explained by the weaker association between IL8 and CIS fatigue compared to EORTC fatigue. Higher levels of the inflammatory z-score including hsCRP were statistically significantly associated with more fatigue. This association is likely driven by levels of hsCRP since the association between the inflammatory z-score excluding hsCRP and fatigue remained non-significant, and with similar effect sizes, after excluding the 24-month time point.

In summary, results from the main analyses add to the existing body of literature on inflammation and fatigue and suggest a link between hsCRP and fatigue. hsCRP can detect low CRP in the blood, and thus can be used to evaluate low-grade inflammation (34, 52). Low-grade inflammation can reduce cellular energy availability and increase energy expenditure, creating an imbalance which possibly explains persistent fatigue (53). CRP is an acute-phase protein mainly upregulated by IL6, and therefore considered a downstream marker for IL6

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activity (52). Other cytokines such as TNFα, IL1, IL1β are also involved in the production of acute-phase proteins (54, 55), and thus require further research as to whether they could be potential targets for intervention (52, 56-58).

In terms of clinical relevance, the observed effect sizes from the fully adjusted models were smaller than the minimal clinically important difference (MCID) defined as 9.3 points for CIS total fatigue (59) and 9 points for EORTC fatigue (60, 61). The largest effect sizes were observed in the analysis with categories of hsCRP where levels >10mg/L were associated with a 6.14 point (95% CI 0.10; 12.19) increase in EORTC fatigue score, compared to levels ≤3mg/L. Results from these analyses provide a better comparison to the MCID as the cut-off values chosen are more clinically relevant than the SD increments used in the main analysis (62, 63). Despite not reaching the MCID, the results provide evidence for a longitudinal association between higher levels of hsCRP and an increase in post-treatment fatigue in CRC survivors.

Results from subgroup analysis indicated that the association between hsCRP and fatigue was only present in men. However, this should be interpreted with caution as the analysis in men had twice the sample size as the women's analysis, rendering the associations in women less stable. Furthermore, most of the interaction terms were non-significant.

One of the strengths of this study was the availability of repeated measurements for both inflammatory markers and fatigue, as well as potential confounders. Additionally, the use of hybrid models to disentangle between- and within-individual associations was important to understand how changes in inflammation within-individuals are, on average, related to fatigue over time. To date, this approach has not been attempted by any of the studies exploring an association between inflammatory markers and fatigue.

A limitation of the present study is its observational nature which does not allow for any causal inference. Moreover, patients with higher levels of fatigue at time of diagnosis may view

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the measurements involved (i.e. filling out questionnaires and blood collection) as being too burdensome. Thus, patients with higher levels of fatigue could be underrepresented in the study, in part explaining the 45% participation rate at diagnosis and potentially causing an underestimation of the true association. Although the participation rate at diagnosis was 45%, our interest was in the association between inflammation and fatigue, specifically in the post-treatment phase, and all follow-up participation rates were high (≥90%). The decrease in sample size as follow-up time increased was mainly due to patients not reaching those time points at the time of data-freeze. Therefore, most participants with missing data are likely missing at random. The smaller sample sizes decrease the power to detect true associations and provide less information on the long-term post-treatment associations of inflammation and fatigue. Additionally, to minimize the potential impact of time of sampling on hsCRP values, which exhibits diurnal variations (64, 65), all samples were collected in fasting individuals during the morning period before breakfast after an overnight fast.

In conclusion, the current study found that higher levels of hsCRP were longitudinally associated with more fatigue in CRC survivors up to 12 months post-treatment. Further longitudinal studies with larger sample sizes will help provide stronger evidence on the long-term association between low-grade inflammation and fatigue post-treatment.

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Table 1 – Demographic, lifestyle, and clinical characteristics of stage I to III colorectal cancer survivors at 6 weeks post-treatment, overall and according to sex.

Baseline characteristics	Total population (n = 237)	Men (n=163)	Women (n=74)
Age, mean (SD)	66.8 (9.2)	66.3 (8.8)	68.1 (9.9)
BMI (kg/m^2)[a], median (IQR)	27.3 (24.4-30.3)	27.3 (24.4-30.4)	27.7 (24.6-29.9)
Use of NSAIDs[b] (yes), n (%)	20 (9.8)	14 (9.8)	6 (9.8)
Physical activity (hours/week), median (IQR)			
LPA	7.5 (2.0-16.5)	6.3 (1.2-12.0)	14.0 (7.0-24.5)
MVPA	7.0 (2.7-14.3)	9.0 (3.5-16.3)	4.1 (1.5-7)
Smoking status (yes), n (%)	22 (9.3)	16 (9.8)	6 (8.1)
Comorbidities n (%)			
0	49 (20.6)	42 (25.8)	7 (9.5)
1	59 (24.8)	43 (26.4)	16 (21.6)
≥ 2	129 (54.4)	78 (47.9)	51 (68.9)
Chemotherapy (yes), n (%)	89 (37.6)	62 (38.0)	27 (36.5)
Radiotherapy (yes), n (%)	64 (27.0)	50 (30.7)	14 (18.9)
Cancer type, n (%)			
Colon cancer	146 (61.6)	94 (57.7)	52 (70.3)
Rectum cancer	91 (38.4)	69 (42.3)	22 (29.7)

[a] Data on BMI is missing for 1 person.
[b] Thirty-three participants have missing data for use of NSAIDs 6 weeks prior to measurement.

Abbreviations: standard deviation (SD), interquartile range (IQR), non-steroidal anti-inflammatory drug (NSAID), light physical activity (LPA), moderate-to-vigorous physical activity (MVPA).

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Table 2 – Fatigue and plasma inflammatory markers in stage I to III colorectal cancer survivors at 6 weeks, 6, 12 and 24 months post-treatment, overall and according to sex.

	Post-treatment follow-up measurements							
	6 weeks n=237[a]		6 months n=184[a]		12 months n=150[a]		24 months n=63[a]	
	Total Population		Total population		Total population		Total population	
	Men n=163	*Women n=74*	*Men n=123*	*Women n=61*	*Men n=104*	*Women n=46*	*Men n=44*	*Women n=19*
Checklist Individual Strength (four subscales), mean (SD)								
Total fatigue	62.9 (26.5)		59.9 (27.3)		53.2 (26.3)		53.0 (25.2)	
20-140	*61.5 (25.9)*	*66.0 (27.9)*	*57.4 (26.6)*	*65.1 (28.0)*	*51.2 (25.4)*	*57.7 (27.9)*	*47.9 (23.7)*	*64.7 (25.3)*
Subjective fatigue	27.3 (13.4)		25.3 (12.9)		22.3 (12.4)		22.2 (13.1)	
8-56	*26.4 (13.3)*	*29.3 (13.6)*	*24.1 (12.6)*	*28.0 (13.2)*	*21.0 (11.8)*	*25.4 (13.2)*	*19.0 (11.9)*	*29.5 (13.0)*
Reduced motivation	12.3 (6.1)		12.1 (6.2)		10.7 (6.1)		10.7 (6.0)	
4-28	*11.9 (5.8)*	*13.0 (6.7)*	*11.3 (5.7)*	*13.6 (7.0)*	*10.1 (5.4)*	*11.9 (7.5)*	*9.7 (5.7)*	*13.1 (6.2)*
Reduced physical activity	10.5 (5.2)		9.6 (5.1)		8.4 (4.9)		8.2 (4.9)	
3-21	*10.7 (5.0)*	*10.2 (5.5)*	*9.6 (5.2)*	*9.7 (4.8)*	*8.5 (4.9)*	*8.0 (4.9)*	*7.7 (4.9)*	*9.5 (4.8)*
Reduced concentration	12.8 (7.2)		12.9 (7.2)		11.8 (6.7)		11.8 (6.3)	
5-35	*12.6 (7.2)*	*13.4 (7.2)*	*12.4 (7.3)*	*13.9 (6.9)*	*11.6 (6.9)*	*12.4 (6.3)*	*11.5 (6.0)*	*12.6 (7.0)*
EORTC QLQ-C30, Fatigue, mean (SD)	29.1 (22.7)		23.6 (22.0)		21.3 (23.6)		20.3 (22.4)	
0-100	*28.3 (23.8)*	*30.9 (20.2)*	*22.0 (23.6)*	*27.0 (18.3)*	*18.2 (22.8)*	*28.3 (24.3)*	*14.6 (19.1)*	*33.3 (24.3)*
Inflammatory markers, median (IQR)								
IL6 (pg/ml)	1.5 (0.8-2.2)		1.3 (0.8-2.1)		0.9 (0.6-1.4)		0.9 (0.5-1.5)	
	1.4 (0.8-2.3)	*1.5 (0.8-2.1)*	*1.3 (0.9-2.3)*	*1.1 (0.8-1.9)*	*0.9 (0.6-1.5)*	*0.8 (0.5-1.2)*	*0.8 (0.4-1.6)*	*1.0 (0.6-1.3)*
IL8 (pg/ml)	5.6 (4.4-7.3)		5.3 (4.4-7.0)		3.9 (3.1-4.8)		4.9 (3.8-7.0)	
	5.5 (4.3-6.8)	*5.9 (4.5-8.1)*	*5.1 (4.4-7.1)*	*5.5 (4.6-7.0)*	*3.9 (3.2-4.8)*	*3.9 (2.9-4.7)*	*4.8 (3.6-5.9)*	*5.2 (4.3-7.7)*
IL10 (pg/ml)	0.4 (0.3-0.5)		0.4 (0.2-0.5)		0.3 (0.2-0.4)		0.2 (0.1-0.3)	
	0.4 (0.3-0.5)	*0.4 (0.3-0.5)*	*0.4 (0.2-0.5)*	*0.4 (0.3-0.5)*	*0.3 (0.2-0.4)*	*0.2 (0.2-0.3)*	*0.2 (0.1-0.3)*	*0.2 (0.1-0.4)*
TNFα (pg/ml)	2.9 (2.4-3.8)		2.8 (2.3-3.6)		2.0 (1.6-2.5)		2.0 (1.6-2.9)	
	2.9 (2.4-3.6)	*3.0 (2.2-4.0)*	*2.8 (2.3-3.7)*	*2.8 (2.3-3.4)*	*2.0 (1.6-2.4)*	*2.0 (1.5-2.6)*	*2.0 (1.6-2.7)*	*2.3 (1.6-3.4)*

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Summary inflammatory z-score[b]	-0.3 (-0.7-0.2)		-0.4 (-0.8-0.2)		-0.3 (-0.8-0.3)		-0.5 (-1.2-1.4)	
excluding hsCRP, median (IQR)	*-0.3 (-0.7-0.2)*	*-0.3 (-0.7-0.2)*	*-0.3 (-0.8-0.3)*	*-0.4 (-0.8-0.1)*	*-0.4 (-0.7-0.3)*	*-0.3 (-0.8-0.1)*	*-0.6 (-1.2-0.9)*	*-0.1 (-1.2-1.8)*
	Patients with data on hsCRP							
	n=200[c]		n=148[c]		n=114[c]		n=0[c]	
hsCRP (mg/L), median (IQR)	2.1 (1.1-5.3)		2.1 (0.8-4.6)		1.7 (0.8-5.3)			
	2.0 (1.0-5.5)	*2.8 (1.7-5.1)*	*2.0 (0.8-4.8)*	*2.2 (0.7-4.4)*	*1.7 (0.7-5.7)*	*1.7 (0.8-4.7)*		
Summary inflammatory z-score including	-0.6 (-1.0-0.5)		-0.5 (-1.1-0.5)		-0.7 (-1.3-0.5)			
hsCRP [d], median (IQR)	*-0.6 (-1.1-0.5)*	*-0.6 (-0.9-0.5)*	*-0.5 (-1.1-0.5)*	*-0.5 (-1.0-0.5)*	*-0.7 (-1.3-0.4)*	*-0.7 (-1.3-0.5)*		

[a] Participants with data available on fatigue, IL6, IL8, IL10, and TNFα.

[b] The inflammatory z-score was calculated as $z = (x - \mu) / \sigma$, in which x is the participant's inflammatory marker value at a given visit, μ is the study population mean, and σ is the study standard deviation, both at given visits. The summary inflammatory z-score for each participant was computed by summing the z-scores of IL6, IL8, TNFα and subtracting IL10.

[c] Participants with data available on fatigue, IL6, IL8, IL10, TNFα, and hsCRP.

[d] The inflammatory z-score was calculated as $z = (x - \mu) / \sigma$, in which x is the participant's inflammatory marker value at a given visit, μ is the study population mean, and σ is the study standard deviation, both at given visits. The summary inflammatory z-score for each participant was computed by summing the z-scores of IL6, IL8, TNFα, hsCRP and subtracting IL10.

Abbreviations: standard deviation (SD), interquartile range (IQR), interleukin (IL), tumor necrosis factor (TNF), high-sensitivity C-reactive protein (hsCRP), European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30).

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Table 3 - Longitudinal associations between inflammatory markers and fatigue in stage I to III colorectal cancer survivors followed-up from 6 weeks to 2 years post-treatment.

		EORTC QLQ-C30, Fatigue β (95%CI)	CIS Total fatigue β (95%CI)	Subjective fatigue β (95%CI)	Reduced motivation β (95%CI)	Reduced physical activity β (95%CI)	Reduced concentration β (95%CI)
IL6	Model I						
	Overall association[a]	**1.85 (0.23; 3.47)**	**2.07 (0.38; 3.76)**	**0.97 (0.12; 1.83)**	**0.49 (0.07; 0.90)**	0.23 (-0.13; 0.60)	0.48 (-0.00; 0.97)
	Intra-individual[b]	1.50 (-0.35; 3.35)	1.40 (-0.44; 3.24)	0.60 (-0.34; 1.54)	0.35 (-0.11; 0.82)	0.08 (-0.34; 0.50)	0.37 (-0.18; 0.91)
	Inter-individual[c]	3.04 (-0.35; 6.44)	**5.44 (1.31; 9.57)**	**2.67 (0.66; 4.67) ***	**1.00 (0.09; 1.92)**	0.74 (-0.01; 1.50)	0.94 (-0.13; 2.01)
	Model II						
	Overall association[a]	**1.69 (0.08; 3.32)**	1.67 (-0.03; 3.36)	0.71 (-0.14; 1.56)	0.36 (-0.05; 0.77)	0.12 (-0.24; 0.49)	0.48 (-0.02; 0.98)
	Intra-individual[b]	1.74 (-0.11; 3.60)	1.28 (-0.60; 3.16)	0.46 (-0.49; 1.41)	0.30 (-0.16; 0.77)	0.05 (-0.37; 0.48)	0.44 (-0.13; 1.01)
	Inter-individual[c]	1.56 (-1.74; 4.86)	3.34 (-0.56; 7.24)	1.71 (-0.19; 3.61)	0.58 (-0.29; 1.45)	0.32 (-0.40; 1.03)	0.62 (-0.44; 1.68)
IL8	Model I						
	Overall association[a]	1.85 (-0.05; 3.76)	0.08 (-1.95; 2.11)	0.36 (-0.66; 1.39)	-0.24 (-0.73; 0.25)	0.08 (-0.35; 0.51)	-0.06 (-0.64; 0.52)
	Intra-individual[b]	1.55 (-0.81; 3.91)	-0.37 (-2.73; 1.98)	0.18 (-1.02; 1.38)	-0.40 (-0.99; 0.18)	0.13 (-0.40; 0.66)	-0.28 (-0.98; 0.42)
	Inter-individual[c]	2.41 (-0.81; 5.64)	1.40 (-2.62; 5.43)	0.84 (-1.11; 2.79)	0.14 (-0.75; 1.03)	-0.03 (-0.76; 0.70)	0.44 (-0.59; 1.47)
	Model II						
	Overall association[a]	**3.34 (0.77; 5.90)**	0.74 (-2.10; 3.57)	0.68 (-0.73; 2.08)	-0.18 (-0.84; 0.49)	-0.03 (-0.61; 0.55)	0.37 (-0.44; 1.18)
	Intra-individual[b]	**3.68 (0.36; 7.01)**	0.25 (-3.21; 3.71)	0.54 (-1.20; 2.28)	-0.43 (-1.27; 0.41)	0.07 (-0.69; 0.83)	0.15 (-0.87; 1.18)
	Inter-individual[c]	3.01 (-0.24; 6.26)	1.40 (-2.50; 5.30)	0.84 (-1.06; 2.75)	0.10 (-0.77; 0.97)	-0.12 (-0.84; 0.60)	0.61 (-0.45; 1.67)
IL10	Model I						
	Overall association[a]	-0.12 (-1.87; 1.62)	0.62 (-1.16; 2.41)	0.12 (-0.79; 1.03)	0.13 (-0.31; 0.57)	**0.53 (0.14; 0.92)**	-0.33 (-0.85; 0.19)
	Intra-individual[b]	0.65 (-1.25; 2.55)	1.41 (-0.48; 3.31)	0.47 (-0.50; 1.44)	0.32 (-0.16; 0.79)	**0.77 (0.35; 1.19) ***	-0.14 (-0.70; 0.42)
	Inter-individual[c]	-4.31 (-8.69; 0.06)	**-5.83 (-11.20; -0.44)**	-2.45 (-5.06; 0.17)	-1.04 (-2.24; 0.15)	-0.77 (-1.76; 0.22)	**-1.49 (-2.89; -0.10)**
	Model II						
	Overall association[a]	-0.07 (-1.80; 1.66)	0.77 (-1.01; 2.54)	0.20 (-0.70; 1.10)	0.14 (-0.30; 0.57)	0.08 (-0.31; 0.48)	-0.29 (-0.82; 0.24)
	Intra-individual[b]	0.76 (-1.09; 2.61)	1.53 (-0.34; 3.39)	0.54 (-0.40; 1.49)	0.33 (-0.13; 0.79)	**0.80 (0.03; 1.57)**	-0.13 (-0.69; 0.44)
	Inter-individual[c]	**-5.90 (-10.74; -1.06)**	**-6.71 (-12.51; -0.92)**	**-2.95 (-5.79; -0.11)**	**-1.40 (-2.69; -0.11)**	-0.81 (-1.87; 0.25)	**-1.57 (-3.14; -0.00)**
TNFα	Model I						
	Overall association[a]	0.32 (-1.90; 2.54)	0.43 (-1.89; 2.75)	0.44 (-0.74; 1.61)	0.39 (-0.17; 0.95)	0.07 (-0.42; 0.57)	-0.41 (-1.08; 0.25)
	Intra-individual[b]	-0.05 (-2.61; 2.52)	0.17 (-2.39; 2.73)	0.39 (-0.92; 1.70)	0.27 (-0.37; 0.91)	-0.01 (-0.59; 0.56)	-0.47 (-1.23; 0.29)
	Inter-individual[c]	1.39 (-2.97; 5.76)	1.58 (-3.85; 7.0)	0.63 (-2.00; 3.25)	0.81 (-0.38; 2.01)	0.33 (-0.65; 1.31)	-0.23 (-1.62; 1.16)
	Model II						
	Overall association[a]	-0.34 (-2.52; 1.85)	-0.13 (-2.43; 2.16)	0.16 (-0.99; 1.31)	0.23 (-0.33; 0.78)	-0.08 (-0.58; 0.41)	-0.45 (-1.13; 0.22)
	Intra-individual[b]	0.10 (-2.45; 2.65)	0.20 (-2.37; 2.78)	0.44 (-0.86; 1.74)	0.28 (-0.36; 0.91)	-0.05 (-0.64; 0.53)	-0.42 (-1.19; 0.36)
	Inter-individual[c]	-1.56 (-5.84; 2.72)	-1.45 (-6.57; 3.67)	-0.86 (-3.36; 1.64)	0.07 (-1.07; 1.20)	-0.16 (-1.09; 0.77)	-0.56 (-1.94; 0.82)

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	Model I						
	Overall association[a]	**2.36 (0.47; 4.25)**	1.13 (-0.69; 2.95)	0.73 (-0.19; 1.65)	0.25 (-0.19; 0.69)	0.03 (-0.36; 0.42)	0.33 (-0.19; 0.85)
	Intra-individual[b]	1.71 (-0.47; 3.89)	-0.07 (-2.11; 1.96)	0.15 (-0.89; 1.19)	-0.05 (-0.56; 0.46)	-0.22 (-0.68; 0.24)	0.05 (-0.56; 0.65)
IZ excluding hsCRP[d]	Inter-individual[c]	**4.28 (0.53; 8.04)**	**5.89 (1.86; 9.92)**	**2.76 (0.81; 4.71)**	**1.18 (0.29; 2.07)**	0.68 (-0.06; 1.41)	**1.17 (0.13; 2.21)**
	Model II						
	Overall association[a]	**2.29 (0.34; 4.24)**	0.74 (-1.13; 2.60)	0.42 (-0.52; 1.36)	0.20 (-0.25; 0.65)	-0.16 (-0.56; 0.24)	0.40 (-0.15; 0.95)
	Intra-individual[b]	2.01 (-0.23; 4.24)	-0.10 (-2.19; 2.0)	0.01 (-1.04; 1.07)	-0.01 (-0.53; 0.50)	-0.31 (-0.79; 0.16)	0.23 (-0.40; 0.86)
	Inter-individual[c]	3.14 (-0.63; 6.91)	3.76 (-0.15; 7.67)	1.79 (-0.13; 3.70)	0.82 (-0.05; 1.69)	0.19 (-0.53; 0.91)	0.89 (-0.17; 1.95)
	Model I						
	Overall association[a]	**3.11 (1.55; 4.68) ***	**3.20 (1.63; 4.77) ***	**1.75 (0.95; 2.54) ***	**0.98 (0.58; 1.37) ***	**0.56 (0.21; 0.90) ***	0.14 (-0.34; 0.62)
	Intra-individual[b]	**2.37 (0.60; 4.13)**	**2.22 (0.51; 3.93)**	**1.33 (0.46; 2.20) ***	**0.77 (0.33; 1.22) ***	0.37 (-0.03; 0.76)	-0.25 (-0.79; 0.30)
hsCRP[e]	Inter-individual[c]	**5.68 (2.45; 8.92) ***	**8.25 (4.40; 12.11) ***	**3.76 (1.86; 5.66) ***	**1.73 (0.89; 2.58) ***	**1.18 (0.47; 1.90) ***	**1.59 (0.55; 2.62) ***
	Model II						
	Overall association[a]	**2.41 (0.72; 4.10) ***	**3.21 (1.42; 5.01) ***	**1.82 (0.94; 2.70) ***	**0.85 (0.41; 1.29) ***	0.38 (-0.01; 0.76)	0.24 (-0.31; 0.78)
	Intra-individual[b]	**2.08 (0.12; 4.04)**	**2.57 (0.53; 4.62)**	**1.62 (0.62; 2.62) ***	**0.73 (0.22; 1.25) ***	0.26 (-0.20; 0.72)	-0.08 (-0.72; 0.57)
	Inter-individual[c]	**3.38 (0.04; 6.73)**	**5.44 (1.61; 9.27) ***	**2.53 (0.63; 4.43) ***	**1.15 (0.32; 1.99) ***	0.65 (-0.07; 1.37)	**1.10 (0.03; 2.17)**
	Model I						
	Overall association[a]	**5.24 (2.88; 7.60)**	**2.82 (0.66; 4.98)**	**1.72 (0.63; 2.80)**	**0.84 (0.31; 1.38)**	0.35 (-0.11; 0.81)	0.33 (-0.31; 0.98)
	Intra-individual[b]	**4.06 (1.26; 6.87)**	0.67 (-1.79; 3.13)	0.78 (-0.47; 2.03)	0.30 (-0.35; 0.94)	-0.06 (-0.62; 0.50)	-0.35 (-1.12; 0.42)
IZ including hsCRP[d,f]	Inter-individual[c]	**8.01 (3.72; 12.29)**	**9.71 (5.35; 14.07)**	**4.47 (2.33; 6.61)**	**2.03 (1.09; 2.97)**	**1.20 (0.39; 2.00)**	**1.90 (0.74; 3.06)**
	Model II						
	Overall association[a]	**4.49 (1.97; 7.01)**	**2.42 (0.06; 4.79)**	**1.40 (0.24; 2.57)**	**0.72 (0.16; 1.29)**	0.04 (-0.46; 0.53)	0.46 (-0.24; 1.17)
	Intra-individual[b]	**3.92 (0.93; 6.91)**	0.69 (-2.07; 3.45)	0.68 (-0.68; 2.04)	0.30 (-0.40; 1.00)	-0.27 (-0.89; 0.36)	-0.01 (-0.87; 0.85)
	Inter-individual[c]	**5.75 (1.39; 10.12)**	**6.71 (2.43; 11.00)**	**3.22 (1.09; 5.35)**	**1.47 (0.55; 2.39)**	0.53 (-0.26; 1.33)	**1.39 (0.20; 2.58)**

Levels of inflammatory markers were divided by their SD at 6 weeks (IL6: SD = 3.15, IL8: SD = 19.57, IL10: SD = 0.86, TNFα: SD = 3.14, IZ excluding hsCRP: SD = 2.08, CRP: SD = 8.19, IZ including hsCRP: SD = 2.62).

Model I: adjusted for age (years), sex (men/women), time since diagnosis (days).

Model II: adjusted for age (years), sex (men/women), time since diagnosis (days), use of NSAIDs (yes/no), BMI (kg/m^2), light physical activity (hours/week), moderate-to-vigorous physical activity (hours/week), comorbidities (0, 1, ≥2), chemotherapy (yes/no), radiotherapy (yes/no), and smoking status (yes/no).

Asterisk (*) represents a significant association after false discovery rate correction for multiple testing.

[a] The beta-coefficient represents the overall longitudinal difference in fatigue score per SD difference of the inflammatory marker. It is a weighted average of the intra- and inter-individual associations.

[b] The beta-coefficient represents the change in fatigue score over time within-individuals per SD increase of the inflammatory marker.

[c] The beta-coefficient represents the difference in fatigue score between-individuals per SD difference of the inflammatory marker.

[d] False discovery rate adjustment for multiple testing not performed.

[e] hsCRP was measured at 6 weeks, 6, and 12 months post-treatment.

[f] Analysis includes patients with data available at 6 weeks, 6, and 12 months post-treatment.

Abbreviations: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), Checklist Individual Strength (CIS), beta-coefficient (β), confidence interval (CI), interleukin (IL), tumor necrosis factor (TNF), high-sensitivity C-reactive protein (hsCRP), summary inflammatory z-score (IZ).

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Figure Legends

Figure 1. Median levels of inflammatory markers (A, B, C, D, E) and fatigue score (F, G) in stage I to III colorectal cancer survivors from 6 weeks to 24 months post-treatment, overall and according to sex.

Figure 2. Forest plots demonstrating beta coefficients and corresponding 95% CI of overall longitudinal associations, including intra- and inter-individual associations, between inflammatory markers and CIS total fatigue (A) and EORTC QLQ-C30 fatigue (B) in colorectal cancer survivors followed-up at 6 weeks, 6, 12, and 24 months after treatment. Asterisk (*) indicates statistically significant associations after false discovery rate correction for multiple testing.

Figure 3. Overall longitudinal associations between levels of hsCRP increments (≤3mg/L, 3-10mg/L, and >10mg/L) with CIS total fatigue (A), EORTC QLQ-C30 fatigue (B), and the CIS subscales – subjective fatigue (C), reduced motivation (D), reduced physical activity level (E), reduced concentration (F), in colorectal cancer survivors followed-up at 6 weeks, 6, and 12 months after treatment. Checklist Individual Strength (CIS) ranges: total fatigue, 20-140; subjective fatigue, 8-56; motivation, 4-28; physical activity level, 3-21; concentration, 5-35. European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) ranges from 0-100.

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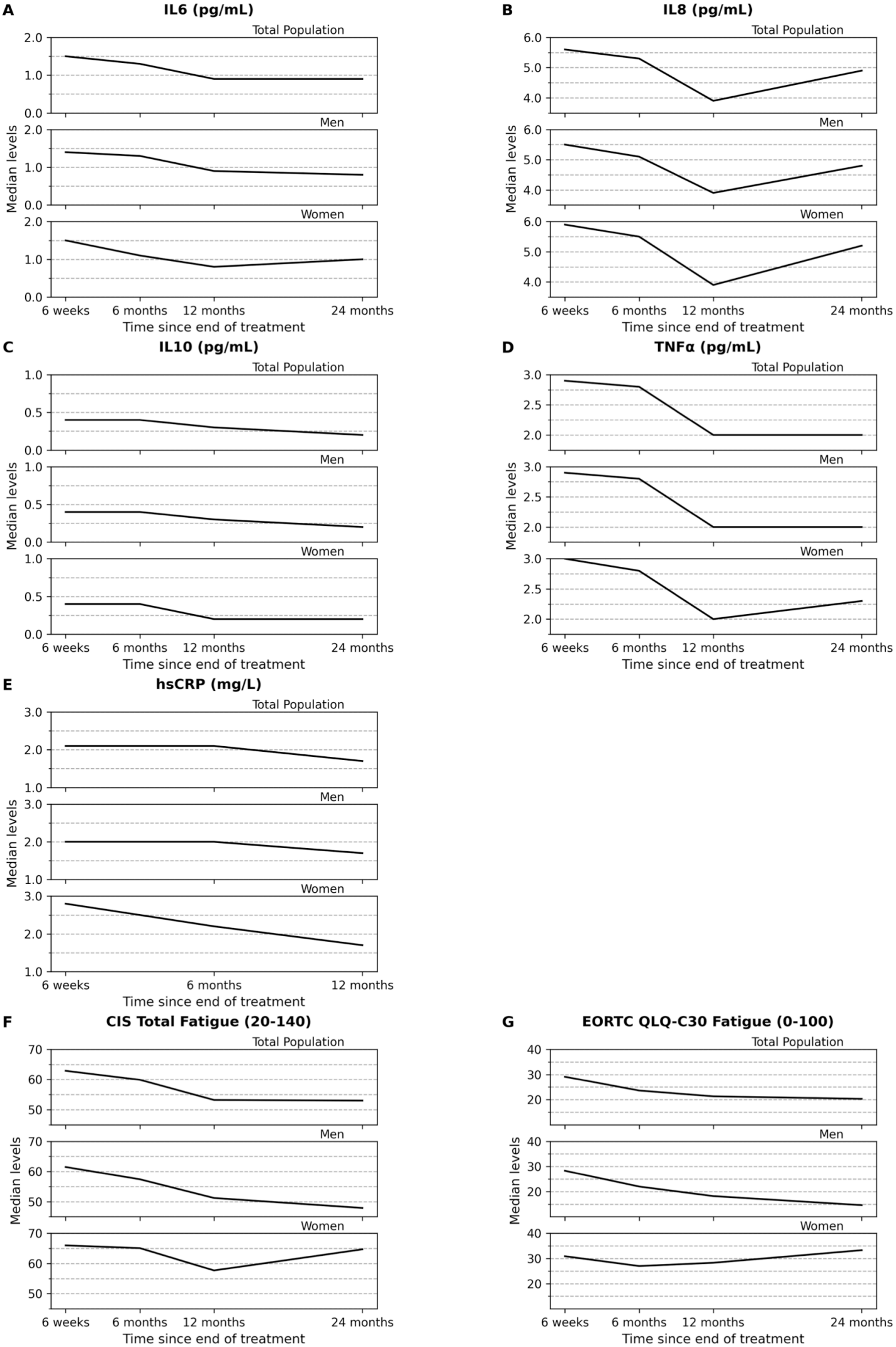

Figure 1

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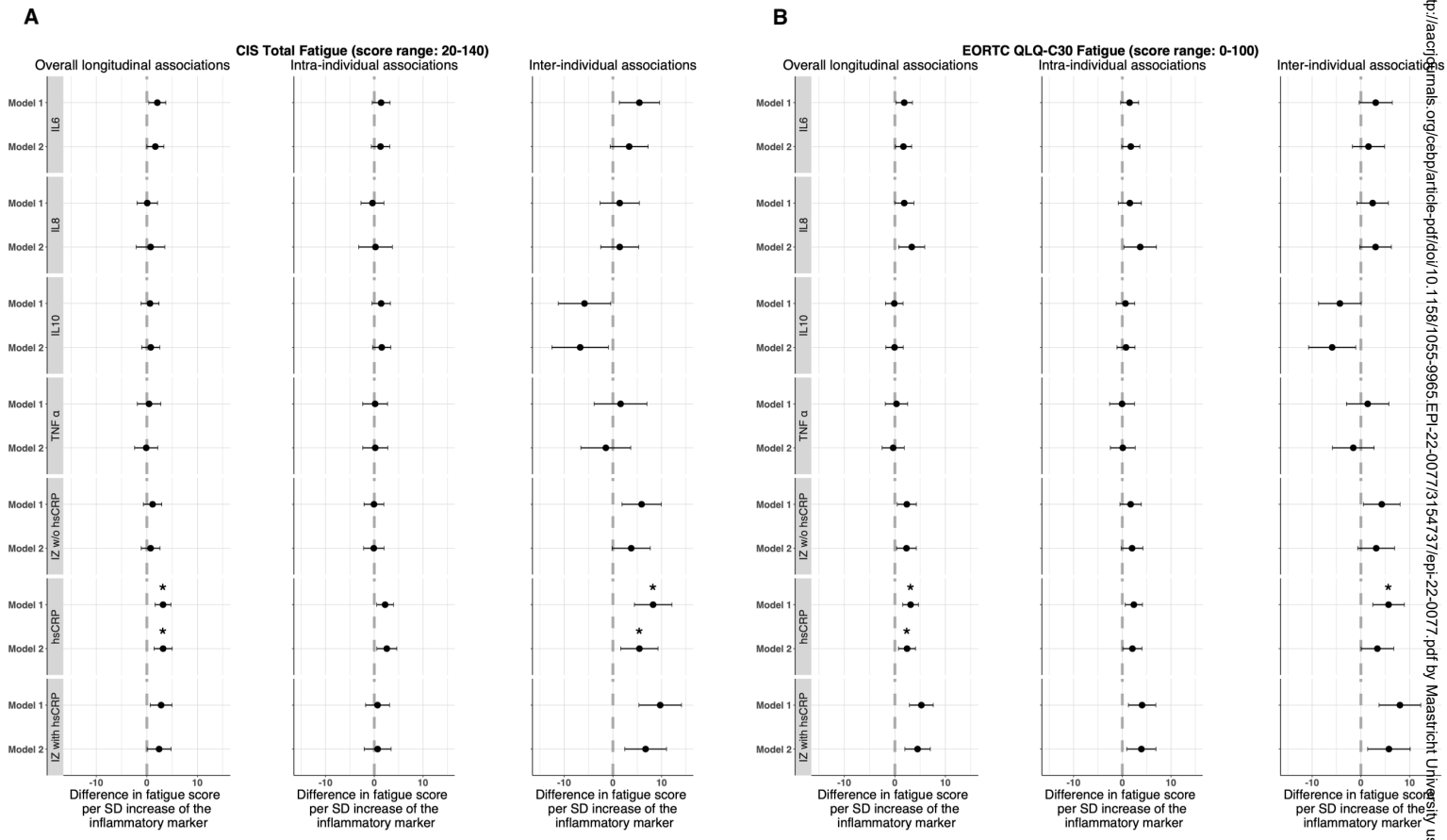

Figure 2

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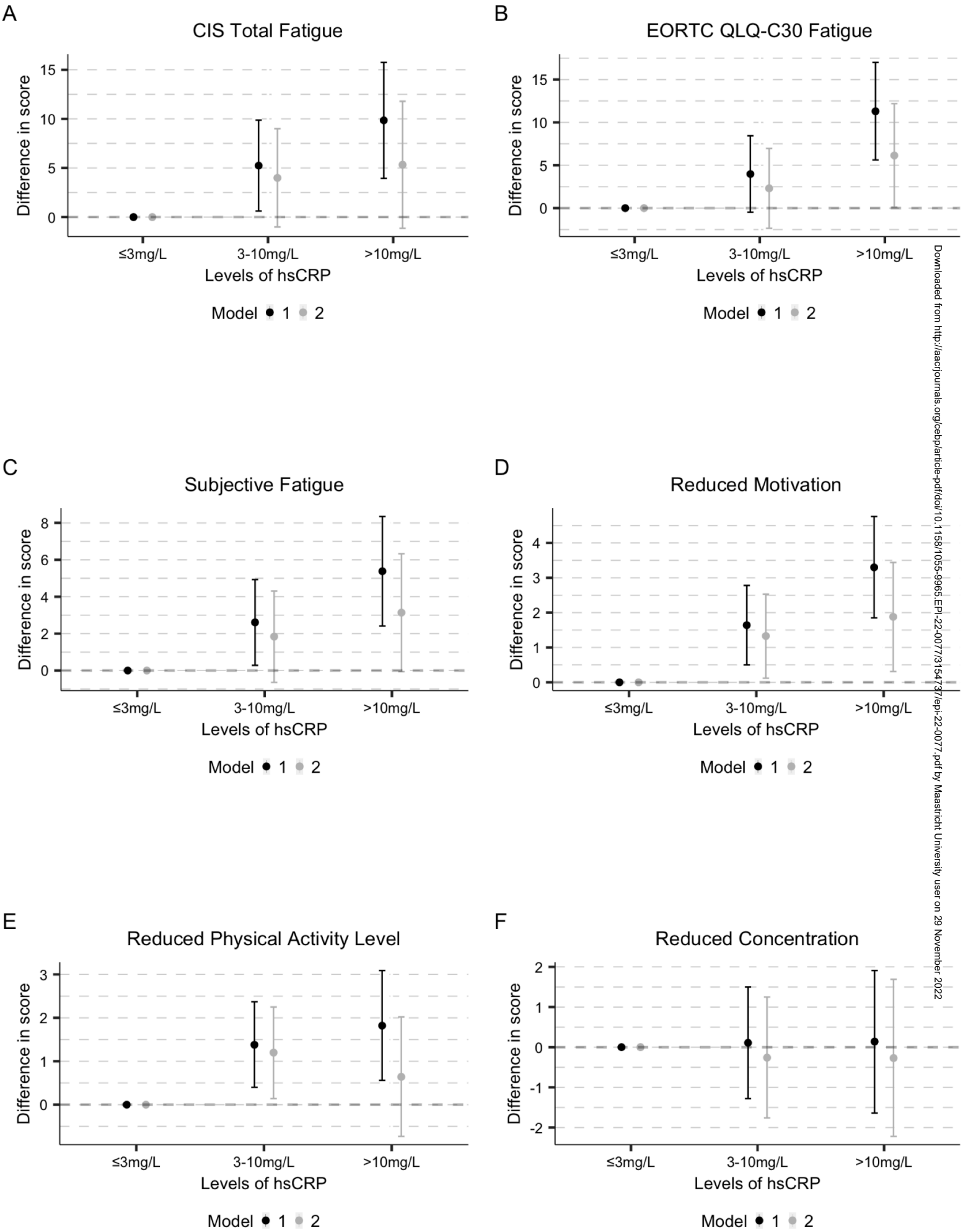

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Figure 3