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Impact of Age on Plasma Inflammatory Biomarkers in the 6 Months Following Mild Traumatic Brain Injury

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Abstract

Objective: To compare plasma inflammatory biomarker concentrations to 6 months in young and older adults with and without mild traumatic brain injury (TBI).

Setting: Level I Trauma Center.

Participants: Younger (21–54 years) and older (55+) adults diagnosed with mild TBI along with age/sex-matched non-injured controls (N=313).

Design: Prospective cohort study.

Main Measures: Multiplex assays were used to quantify concentrations of selected plasma inflammatory markers at Day 0, Month 1 and 6.

Results: Persistent aging related differences were found between control groups in concentrations of four cytokines up to 6 months. At day 0, IL-6, IL-8 and fractalkine were higher in the older TBI compared to older control as well as the younger TBI groups, while IL-10 was higher in older TBI compared to controls. At month one, significantly higher concentrations of IL-8, fractalkine and TNF-alpha were seen. At 6 months post-injury significantly higher concentrations of IL-6 and IL-8 were seen, while a lower concentration of IL-7 was found in older versus younger TBI groups.

Conclusion: The neuroinflammatory signature that accompanies mild TBI in older adults differs from that of younger adults. The differences seen are notable for their roles in neutrophil attraction (IL-8), neuronal-microglial-immune cell interactions (fractalkine), and chronic inflammation (IL-6).

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According to the Centers for Disease Control and Prevention, traumatic brain injury (TBI) is a “silent” epidemic that affects more than 2.87 million persons in the US annually.[1] Within this silent epidemic, there is a growing, yet understudied, population of concern, the older adult. Injuries in older adults account for more than 22% of all incident TBIs, despite the fact that they comprise only about 13% of the total population.[2] The vast majority of these brain injuries (>75%) are classified as mild.[1] Despite efforts to highlight prevention of brain injury in the Healthy People 2020 initiative, the incidence of TBI continues to increase, especially in persons older than 65.[2] Not only do older adults experience TBI at disproportionately higher rates, their outcomes following injury have been reported to be worse than younger patients with similar injuries.[3,4] Prior studies have shown that as we age our ability to regenerate nerve tissue and recover from a brain injury diminishes, potentially contributing to the negative outcomes seen in these individuals compared with younger adults.[4,5] There is limited work examining the effects of the physiologic changes associated with aging which may influence pathophysiologic responses and subsequent outcomes following TBI in humans. We hypothesize that aging may contribute to the pathological response to TBI in older adults by modulating the inflammatory response. This is important to study, as the natural history of inflammatory cytokine expression following injury is not well characterized in large clinical samples of older adults.[6,7]

Inflammation is one of the primary responses of the brain to TBI. Inflammatory mediators such as cytokines and chemokines are released both locally at the site of injury and systemically in response to injury.[8,9] Increases in proinflammatory chemokines and cytokines have been reported following experimental and clinical TBI and may be related to sequelae of injury.[10–12] For example, IL-1β may exacerbate injury by potentiating leukocyte recruitment to the site of central nervous system injury. In a transgenic mouse model, sustained overexpression of IL-1 β was reported to be responsible for localized, persistent leukocyte infiltration within the brain parenchyma.[13] Administration of additional IL-1β at 30 minutes or 24 hours post injury also worsened contusion volume and increased loss of hippocampal neurons in rat.[9] In humans following isolated TBI (n=48), serum IL-1β concentrations significantly correlate with Glasgow coma scale and Glasgow outcome score.[14] However, no correlation was found between parenchymal levels of IL-1β obtained from microdialysis and outcome in a small sample of 12 subjects.[15] At this time, there remains much debate over the role of specific inflammatory mediators in TBI.[10,11]

Aging is a pathological state. The stochastic theory of aging posits that various factors such as molecular damage via free radical accumulation, changes in gene expression over time, genetic damage, and mitochondrial dysfunction cause progressive neurodegeneration. Aging itself has been associated with a proinflammatory state, and aging related elevations in cytokine concentrations have been reported.[16–19] Peripheral increases in certain cytokines (IL-6, TNF-α) in older adults have been associated with conditions of aging such as macular degeneration, atherosclerosis, heart failure, stroke, cognitive impairment, as well as declines in muscle strength and frailty.[20–26] Further, persistent inflammation has been associated with increased morbidity and mortality in older adults.[16,21] Age-related increases in IL-1β have been reported in the hippocampus of the rat and are associated with changes in long term potentiation[27] and memory.[28] In the rat, age-related decreases in fractalkine mRNA and protein expression have also been reported in the hippocampus, which are accompanied by

increases in IL-1β.[29,30] These changes may indicate a "homeostatic shift" in the aged brain, denoted by increased reactivity to stress indicated by increased numbers of activated and primed microglia which may produce higher concentrations of cytokines when stimulated, resulting in a larger neuroinflammatory response, increased neuronal injury and impairment.[28]

Peripheral increases in cytokines in aging populations have generally been predictive of disease and outcome across studies in various conditions; however, much less is known about the inflammatory response to TBI in the aged brain. While plasma granulocyte colony-stimulating factor (G-CSF) was found to be elevated in the first 24 hours following mild-moderate TBI in adults compared to non-injured controls, this elevation was blunted in persons older than 55 years of age.[31] G-CSF promotes production of neutrophils, has neuroprotective properties and has been associated with improved functional outcome and reduced lesion volumes in other forms of brain injury.[31] Work in an experimental model of brain injury found increased mRNA levels of pro-inflammatory cytokines IL-1β, IL-6, and TNF-α (> 3 times relative control) at 6 hours post-injury in aged compared to adult rats.[32] In another study using controlled cortical impact (CCI) in aged mice, the permeability of the blood-brain barrier was found to be significantly more compromised than in adult animals (5–6 months).[34] This could be important to movement of molecules, such as cytokines, across the blood-brain barrier. In the same CCI model, differential gene expression of TNF-α in aged animals was seen at one day post-injury in thalamus (4.6 fold over basal levels).[35] This level was significantly higher than young brain-injured animals (3.8 fold). In addition, Interferon-γ levels were reduced in aging brain injured mice at 1 and 3 days post-injury compared to young mice.[35] Our review of the literature has identified a paucity of studies in older humans; therefore, this is a gap in knowledge.

Older adults are at higher risk for TBI and TBI-related disability. However, we have limited knowledge about differences in the pathophysiologic response to TBI that result from age-related changes. In this study, we examine the neuroinflammatory response following TBI in younger and older adults. We hypothesized that a heightened acute proinflammatory response and sustained chronic inflammatory response would be more likely to occur in older adults following mild TBI.

METHODS

Study Design:

A prospective 4-group cohort design was used to assess the effects of aging and TBI on inflammatory makers. Older adults (> 55 years of age) with mild TBI (Group 1) were enrolled in an equal number in each of three comparison groups: younger adults (21–54 years of age) with mild TBI (Group 2), non-injured older adults (> 55 years of age) (Group 3) and non-injured young adults (21–54 years of age) (Group 4). Groups 3 and 4 were age (+/− 3 years) and sex-matched to the TBI participants enrolled in Groups 1 and 2.

Settings, Recruitment and Screening:

Older adult and younger adult TBI study participants (Groups 1 and 2) were recruited prospectively in a consecutive manner from persons seeking care at a Level 1 Trauma Center. Healthy non-injured older and younger adults (Groups 3 and 4) were recruited from the community. For full details on recruitment and screening please see Thompson et al.[36]

In brief, to be eligible for this study, persons in Groups 1 and 2 must have received a clinical diagnosis of mild TBI (via CDC criteria) within the past 24 hours. In order to better distinguish the inflammatory effects of TBI from other non-head injury, we excluded persons with injuries to other body regions that were classified as greater than a moderate injury (using listing of abbreviated injury scale (AIS) codes >2). As the following conditions significantly alter the recovery pattern from mild TBI, we excluded persons who have cervical spine trauma at time of injury; previous head injury or stroke in the past year; or with a diagnosis of dementia. As specific drugs alter cytokine concentrations, we excluded persons with use at time of screening of oral or injectable steroids within the last 30 days; biologic inhibitors of cytokines, immune suppressive agents; NSAIDS more than 3 days per week; or COX-2 inhibitors. To be eligible, control subjects (Groups 3 and 4) must have been able to independently perform activities of daily life; speak and read English and lived in Western Washington State. We excluded those individuals who had a prior head injury or stroke; diagnosed dementia; had been hospitalized in the past 6 months; as well as the specific drug categories noted above. All participants provided written informed consent to participate, and study procedures were approved by the University of Washington's Institutional Review Board.

PROCEDURES

Older and Younger Participants with Traumatic Brain Injury (Groups 1 and 2):

Blood samples were collected from participants at time 0 in hospital by licensed personnel following enrollment. The timing for the initial day 0 sample was as close as possible to time of admission to the emergency department and was within 24 hours of injury. Data on demographics, injury data (type, location, mechanism, and severity) and comorbid conditions were extracted from the medical record. Blood samples were again collected from participants at 1 and 6 months post-injury.

Older and Younger Control Participants (Groups 3 and 4):

For participants in Groups 3 and 4, interested participants identified self to study staff and underwent phone screening for eligibility. Following phone screen, an initial visit was scheduled. At this visit and following written informed consent, participants answered demographic questionnaires and a blood sample was obtained. Blood samples were again obtained at 1 and 6 months post-enrollment.

Blood sampling procedures:

blood was collected from each subject and used for the detection of inflammatory cytokines using 2–6mL EDTA-anticoagulated blood tubes (Becton Dickinson, Franklin Lakes, NJ). Samples were transported by the research team and processed for plasma within 2 hours of

collection. All blood draws after Day 0 in participants with TBI, and all draws in control participants were completed before 10:00AM to minimize circadian variability. Plasma samples were stored at −70°C until batch evaluation.

Multiplex Cytokine Assays:

Multiplex cytokine assays, using a fluorescent microsphere suspension array on the the Bio-PlexTM Suspension Array System (Bio-Rad Laboratories; Hercules, CA), were used to detect and quantitate protein concentrations of selected inflammatory chemokine/cytokines. Commercially available kits were used (Milliplex MAP hs13-plex cytokine and Milliplex 2-plex kits, Millipore). All measures were run in duplicate using the overnight protocol. Lab personnel were blinded to case or control status. Quality controls included the use of a pooled sample across all plates tested to assess inter-assay variability. Mean value of the paired observed concentration was used for analysis of each analyte.

STATISTICAL ANALYSIS

Measurements of inflammatory cytokines were log-transformed in order to obtain normality of distribution within groups. Means, standard deviations and distributions werre to describe inflammatory biomarkers at each time point. Linear mixed models for longitudinal data was used to estimate the average inflammatory biomarker concentrations across time for the four groups. This model allows for estimating the response to injury relative to a non-injured control for both younger and older adults. An alpha of 0.05 was set. Effect sizes were then calculated using Glass's delta.

RESULTS

Three-hundred thirteen participants enrolled in the study. The average age of younger participants with mild TBI (n=96) was 35 years (SD 9.4), while older participants with TBI (n=75) were 66.5 years of age on average (SD 8.9). Both groups were predominantly male (62.5% and 65.3%, respectively). Due to matching, controls had similar age and sex distribution (Table 1). Older persons with mild TBI in the sample were more likely to have received pre-hospital care and were more likely to be admitted to the intensive care unit than younger adults with TBI (Table 1). However, there was no difference between groups in the percentage of participants with positive CT scan on admission (Table 1).

We first examined the effect of aging alone on cytokine concentrations over time by comparing older to younger age andsex-matched controls. Persistent age-related differences were found between control groups in the concentrations of five cytokines from baseline to 6 months: IL-2, IL-5, IL-8, TNF-alpha, GM-CSF (See Table 2; Supplemental Digital Content Table 1). We then examined the influence of TBI by comparing cytokine concentrations of younger persons with mild TBI to their controls, as well as those of older adults following TBI to their control group. Within 24 hours of injury, concentrations of IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, GM-CSF, IFN-Ɣ, and TNF-α were significantly elevated above that of controls (See Table 2; Supplemental Digital Content Table 1). At 6 months, only IL-5, IL-7, IL-8, IL-12, GM-CSF and TNF-α concentrations persisted above that of controls. In contrast, while similar elevations were seen across time compared to

younger controls in all cytokines noted at 24 hours, when examining differences compared to similar aged controls, only IL-6, IL-8 and IL-10 had a significant elevation. Notably, fractalkine was higher in only in older persons following TBI compared to older controls at <24 hours post-injury and 6 months (Table 2).

We then compared the patterns of neuroinflammatory signatures that accompany mild TBI in persons without other significant extracranial injuries across time in older and younger individuals. At <24 hours post-injury, IL-6, IL-8 and fractalkine concentrations were significantly higher in older persons with mild TBI compared to younger adults with mild TBI. At one month, significantly higher concentrations of IL-8, fractalkine and TNF-alpha were seen. At 6 months post-injury, significantly higher concentrations of IL-6 and IL-8 were seen, while a lower concentration of IL-7 was found in older versus younger TBI groups (Table 2). The largest effect size was seen in fractalkine concentrations (1.0, .27 and 2.2 at day 0, month 1 and 6, respectively) when comparing older TBI to their age-matched controls. This was followed in order by by IL-8, IL-5 (medium), IL-6 and IL-7 (small). In contrast, in younger adults with mild TBI, the largest effect was seen in IL-7.

DISCUSSION

Our results revealed insights to the inflammatory response in younger and older mild TBI adults over 6 months. Plasma samples were collected at three time points (day 0, months 1 and 6) in younger and older adults with and without mild TBI. Inflammation following TBI is a complex and dynamic process of both the central and peripheral nervous systems, which may be influenced by age. In this study we evaluated inflammatory cytokines and chemokine profiles in the acute and post-acute phase of mild TBI. Our findings addressed the complex nature of how age influences the chronic recovery phase of TBI in adults. Our data suggests that TBI has particular age-related neuroinflammatory signatures that differ in older and younger adults experiencing mild TBI.

Pro- and anti-inflammatory cytokine profiles in serum and cerebrospinal fluid (CSF) have previously been reported within 24 hours following TBI, specifically IL-6 and IL-8.[37–41] Our results demonstrated similar elevated concentrations of IL-6 and IL-8 in both younger and older mild TBI groups within the first 24 hours but also throughout the study to 6 months. IL-6 has pro- and anti-inflammatory cytokine properties and is known to regulate inflammation, immunity, and neural development.[42] Elevated plasma IL-6 concentrations have been seen within the first 24 to 48 hours following severe TBI injury and associated with severe brain injury, poorer outcomes, and a greater risk for mortality.[43–45] IL-8 is a pro-inflammatory cytokine and is produced primarily by monocytes and macrophages and acts as a chemoattractant for neutrophils.[46] Studies show that IL-8 measured in serum and CSF of persons within 24 hours of severe TBI is associated with increased risk for mortality.[47,48] Yan et. al (2014) collected CSF and serum samples (n = 42) over 5 days and measured IL-8 concentrations.[49] The highest concentrations were seen within 24 to 48 hours post-injury in adults following severe TBI.[49]

Limited studies have evaluated IL-5 and IL-7 in TBI. IL-5 is secreted by Th2 cells and regulates eosinophil development.[50–53] A shift in patterns of T-helper cells to type 2 (Th2)

has been seen in the sub-acute phase post-traumatic injury, and is associated with a counter-inflammatory response to trauma.[54] IL-5 is thought to be beneficial in the repair of brain damage and suppression of inflammation.[55] IL-7 is required for T-cell development, function and survival and may play a role in wound healing.[56–58] IL-7 signaling occurs through the Jak-Stat pathway and promotes T-cell survival through upregulating anti-apoptotic genes.[56] Juengst and colleagues (2015) found significantly elevated IL-7 concentrations in CSF within the first week in adults experiencing moderate to severe TBI (n = 41) compared to healthy controls (n = 15), while no differences were found in IL-5 concentrations.[59] Overall our results revealed elevated plasma IL-5 and IL-7 seen in both younger and older adults following mild TBI compared to younger controls throughout 6 months. Interestingly, a lower concentration of IL-7 was found in older persons with mild TBI compared to younger adults experiencing TBI at 6 months. Our findings confirm and extend prior work in those who have experienced moderate-severe TBI to those experiencing mild injury as well as extending to chronic time periods post-injury. Additionally, we identify age-related differences that should be explored in future studies across all severities of brain injury as well as to examine the role of these changes on outcome.

We found elevated fractalkine concentrations throughout 6 months in a larger sample of older TBI adults in our study, but did not see a similar difference in younger adults following mild TBI. Fractalkine (CX3CL1) is the only chemokine that has a sole receptor (CX3CR1) and is expressed on neurons which directly regulates microglia.[60–63] Via this interaction, it promotes microglial activation and migration to the site of injury and increases other leukocytes in response to injury. In studies of mice deficient for fractalkine or its receptor, ischemic injury has been shown to result in smaller infarct volumes and improved mortality compared to wild type animals. Fractalkine has also been associated with the development of pain syndromes through induction of the proinflammatory cytokine IL-1, thus it may play a role in symptom development following TBI. Rancan et al., (2004) found higher concentrations of fractalkine from serum than CSF samples in patients with severe TBI (mean age 36 years old; n = 12) compared to controls (n=13) at baseline which declined over 14 days.[64] The differences between the present report and the study by Rancan and colleagues could be related to differences in detection assay methods (serum vs. plasma, ELISA vs. Multiplex, antibody manufacturer and differences in the two samples (age, injury severity).

Limitations of the present report include recruiting from a single site, which limited the racial/ethnic diversity of the sample based on the population served by the facility. Another potential limitation is that peripheral blood samples, rather than a more direct measure of cerebral inflammation such as cerebral spinal fluid, were used to examine the inflammatory response post-TBI. Obtaining cerebral spinal fluid from persons following mild TBI was not chosen due to risk and patient burden, and blood samples are obtained in the ED as part of usual care. Further, by limiting the sample to those with AIS scores of 2 or less in areas other than the head, we reduced the potential influence of non-cranial injuries on the inflammatory measures. We obtained blood samples as soon as possible after enrollment in those with mild TBI to ensure within 24 hours of injury. This may have increased variability in the Day 0 cytokine concentrations in the mild TBI groups as there is normally circadian regulation of innate immunity.

CONCLUSION

The present report extends prior literature by examining differences across age groups and focusing on persons following mild TBI to 6 months post-injury. Most prior studies examining the inflammatory response have focused on the acute phase post-injury, but given the proinflammatory state that accompanies aging, it was important to study longer-term outcomes to examine the chronic phase post-injury. The neuroinflammatory signature that accompanies mild TBI in older adults differs from that of younger adults. The differences seen are notable for their roles in neutrophil attraction (IL-8), neuronal-microglial-immune cell interactions (fractalkine), and chronic inflammation (IL-6). It will be important to examine these differences in relation to symptoms and functional recovery in future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Conflicts of Interest and Source of Funding:

Dr. Thompson received grant funding for the work FROM the NIH/NINDS 1R01NS07791 and Dr. Martha is currently supported by NIH/NINR T32NR016913 as a post-doctoral fellow. There are no conflicts of interest to report. For the remaining authors, none were declared.

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Table 1.

Description of Participant Demographics and Care Characteristics.

	Total Sample N=313	Younger Control n=80	Older Control n=62	Younger TBI n=96	Older TBI n=75	p-value†
Age Mean(SD)	48.7(18.0)	35.1(10.0)	65.7(8.1)	35.0(9.4)	66.5(8.9)	<0.0001
Male sex	201(64.2)	52(65.0)	40(64.5)	60(62.5)	49(65.3)	0.98
Race						0.71
White	254(81.2)	63(78.8)	50(80.7)	76(79.2)	65(86.7)	
Black/African American	33(10.5)	10(12.5)	5(8.1)	12(12.5)	6(8.0)	
American Indian/Native American	3(1.0)	0(0.0)	0(0.0)	2(2.1)	1(1.3)	
Asian/Pacific Islander	15(4.8)	5(6.2)	5(8.0)	4(4.2)	1(1.3)	
Other	8(2.6)	2(2.5)	2(3.2)	2(2.1)	2(2.7)	
Hispanic Ethnicity	13(4.1)	4(5.0)	0(0.0)	8(8.3)	1(1.3)	0.02
Pre-hospital care received	135(85.4)	NA	NA	70(79.5)	65(92.9)	0.02
Positive CT scan						
Yes	41(32.5)	NA	NA	19(31.7)	22(33.3)	0.84
No	85(67.5)	NA	NA	41(68.3)	44(66.7)	
Hospital length of stay Mean (SD)	1.3(2.6)	NA	NA	1.2(3.2)	1.4(1.8)	0.55
ICU admission						0.02
No	129(81.1)	NA	NA	77(87.5)	52(73.2)	
Yes	30(18.9)	NA	NA	11(12.5)	19(26.8)	

†Difference reported across all four groups for age, sex, race, ethnicity, and between younger and older TBI for all other characteristics.

All data are presented as n (%) except as noted. NA=not applicable.

Table 2.

Comparison of Natural Log-transformed Values of Selected Inflammatory Biomarker Concentrations in Younger (aged 21–54 years) and Older (55 years and above) Individuals with mild Traumatic Brain Injury and Age/Sex Matched Controls.

Inflammatory Biomarker	Older Control vs. Younger Control (Effect of Aging)	Younger TBI vs. Younger Control (Effect of TBI)	Older TBI vs. Younger Control (Effect of TBI + Aging)	Older TBI vs. Older Control (Effect of TBI in context of Aging)	Older TBI vs. Younger TBI (Effect of Aging in context of TBI)
IL-5					
Day 0	0.26 (0.01,0.51)*	0.44 (0.19,0.69)*	0.36 (0.11,0.61)*	0.10 (−0.16,0.36)	−0.08 (−0.34,0.18)
1 month	0.26 (0.05,0.48)*	0.16 (−0.08,0.40)	0.25 (0.01,0.50)*	−0.01 (−0.25,0.23)	0.09 (−0.17,0.35)
6 months	0.36 (0.09,0.62)*	0.33(0.07,0.58)*	0.29 (0.04,0.54)*	−0.07 (−0.31,0.18)	−0.04 (−0.27,0.19)
IL-6					
Day 0	0.26 (−0.01,0.53)	1.39 (1.08,1.70)*	1.78 (1.46,2.11)*	1.53 (1.24,1.82)*	0.40 (0.07,0.72)*
1 month	0.21 (−0.06,0.48)	0.19 (−0.09,0.47)	0.41 (0.11,0.70)*	0.20 (−0.06,0.45)	0.21 (−0.05,0.48)
6 months	0.22 (−0.06,0.49)	0.07 (−0.20,0.34)	0.31 (0.06,0.57)*	0.10 (−0.15,0.34)	0.25 (0.01,0.48)*
IL-7					
Day 0	0.06 (−0.20,0.31)	0.49 (0.26,0.72)*	0.26 (0.03,0.48)*	0.20 (−0.06,0.46)	−0.24 (−0.48,0.01)
1 month	0.09 (−0.15,0.32)	0.29 (0.08,0.50)*	0.15 (−0.08,0.37)	0.06 (−0.18,0.30)	−0.14 (−0.36,0.08)
6 months	0.14 (−0.11,0.38)	0.33 (0.12,0.55)*	0.09 (−0.14,0.31)	−0.05 (−0.29,0.19)	−0.25 (−0.45,−0.04)*
IL-8					
Day 0	0.33 (0.15,0.50)*	0.54 (0.38,0.71)*	0.94 (0.72,1.16)*	0.62 (0.39,0.84)*	0.40 (0.18,0.61)*
1 month	0.32 (0.15,0.49)*	0.19 (0.02,0.35)*	0.45 (0.27,0.63)*	0.13 (−0.04,0.30)	0.26 (0.10,0.42)*
6 months	0.31 (0.15,0.47)*	0.21 (0.05,0.36)*	0.43 (0.25,0.60)*	0.12 (−0.06,0.30)	0.22 (0.04,0.39)*
Fractalkine (CX3CL1)					
Day 0	−0.35 (−0.77,0.08)	−0.20 (−0.56,0.16)	0.40 (0.03,0.78)*	0.75 (0.27,1.24)*	0.61 (0.18,1.04)*
1 month	−0.34 (−0.78,0.11)	−0.31 (−0.67,0.05)	0.13 (−0.24,0.50)	0.47 (−0.02,0.96)	0.44 (0.04,0.85)*
6 months	−0.28 (−0.75,0.18)	−0.11 (−0.49,0.28)	0.32 (−0.15,0.79)	0.60 (0.07,1.14)*	0.42 (−0.05,0.90)

*= p<0.05 on post-hoc comparison.

IL: interleukin; Inflammatory biomarker concentrations are presented as difference (95% CI), comparator group listed last