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Research Article

Effects of a Mindfulness-Based Intervention on Circulating Cytokine Levels in Individuals with Amnestic Mild Cognitive Impairment: A Pilot Study

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Abstract

Peripheral inflammation plays an important role in the pathophysiology of Alzheimer's disease (AD) and dysregulations in circulating levels of different inflammatory mediators are detectable as early as the mild cognitive impairment (MCI) stage towards AD. Depressive symptoms, another risk factor of AD, are often found in individuals with MCI and associated with heightened levels of peripheral inflammatory mediators. Diminution in depressive symptoms and alterations of peripheral inflammation profiles have been observed following Mindfulness-based interventions (MBIs). In this pilot randomized-control trial, the impact of a mindfulness-based intervention (MBI) was compared to that of a psychoeducation-based intervention (PBI) on the peripheral inflammation profile and depressive symptomatology of participants with MCI. Plasma samples and scores on the Geriatric Depression scale (GDS) were obtained from 12 participants per group before and after the 8-week interventions.

Flow cytometry allowed for inter-group comparisons of the pro-inflammatory cytokines Interleukin (IL)-6 and Tumor Necrosis Factor (TNF)-α levels. Post-MBI, two tendencies stand out regarding inflammation profiles: 1) a decrease of TNF-α for participants having higher initial levels of this cytokine, and 2) an increase of IL-6 levels for all participants. In the PBI group, the cytokine levels remained unchanged post-intervention. Regarding depressive symptomatology, no significant variations were noted for both groups. Moreover, variations on depressive symptoms and peripheral levels of cytokines were not correlated. MBI could exert a physiological effect on an important feature of AD, namely inflammation. Furthermore, action mechanisms behind physiological and psychological effects of MBIs could stem from independent sources. This remains to be demonstrated with more robust data.

Keywords
Mindfulness; mild cognitive impairment; Alzheimer's disease; peripheral inflammation; cytokines; interleukin-6; tumor necrosis factor alpha; depressive symptoms

1. Introduction

Alzheimer's disease (AD) is characterized by cognitive decline (most commonly involving memory deficits), with significant impairment of activities of daily living [1]. No effective treatment is currently available to reverse or stop the progression of AD. In light of the many failed attempts at developing effective treatments, hope is now put in primary and secondary prevention strategies targeting modifiable risk factors of AD such as depression, anxiety, smoking, diabetes, hypertension, obesity, cognitive inactivity, low educational attainment, physical inactivity, and inflammation at early stages of the disease [2-7].

Peripheral inflammation as a modifiable risk factor of AD has ramifications crucial for the evolution of the disease. First, inflammation is an underlying common denominator of multiple other risk factors of AD [8, 9]. As illustrated by the allostatic load theory [10], the accumulation of adverse factors (e.g. depression, anxiety, hypertension) over time may impact the homeostasis of the immune system by promoting a chronic state of low-grade systemic inflammation [9]. Second, this chronic inflammatory state may actively contribute to the pathophysiological processes of AD and their repercussions in the brain. Indeed, neuroinflammation, an otherwise beneficial defense mechanism of the brain, becomes chronically overactivated in AD and damages brain tissues, therefore contributing to neurodegeneration and progression of the disease [11, 12].

A growing body of evidence indicate that systemic blood levels of pro-inflammatory cytokines are elevated in AD patients compared to healthy controls, particularly interleukin (IL)-6 and tumor necrosis factor (TNF)-α [13]. Heightened levels of these cytokines increase the risk for developing AD and tend to increase to higher ranges as the disease progresses, making them potential candidates as biomarkers of AD [13, 14]. Some studies reported heightened levels of these cytokines, but to a lesser extent, in individuals suffering from Mild Cognitive Impairment (MCI) when compared to healthy controls [15-18].

MCI corresponds to the prodromal phase of AD in a large subset of individuals [19]. Cognitive functioning in MCI is inferior to what can be expected for the age and level of education of the person, but not sufficient to cause a significant impact on daily functioning [20]. Individuals with MCI are excellent candidates for AD secondary preventive strategies since they show early signs or characteristics of the disease on which one can intervene.

Interventions that target inflammation are believed to be more effective for AD prevention in people at risk if they are conducted early in the progression of the disease [21]. According to a multicentric longitudinal study by Breitner and collaborators [22], asymptomatic elderly with a genetic AD predisposition who took nonsteroidal anti-inflammatory drugs (NSAIDs) daily over the course of two years had a lower risk of developing AD within the next two to three years. However, taking NSAIDs at later stages of AD has been associated with an acceleration of the disease progression, suggesting that the preventive effects of NSAIDs could be limited to the early stages of the disease. Epidemiological studies concurred with a diminution in incidence [23-27]. Despite their prevention effects on cognitively healthy older adults, long-term use of these drugs are often accompanied by incommoding or even dangerous side effects. [28]. Therefore, alternative methods might be favored to target inflammation in individuals with MCI.

Mindfulness-based interventions (MBIs) are amongst the alternative methods that could be used to reduce inflammation in MCI. Mindfulness programs generally stem from the Mindfulness-Based Stress Reduction (MBSR) program of Jon Kabat-Zinn [29]. These include different types of meditation practices where individuals cultivate the ability to pay attention to the present moment in a non-judgmental way. MBIs are accessible and have limited negative side effects, as is the case of other psychosocial interventions bringing to consciousness the presence of negative experiences. A meta-analysis indicated a decrease of circulating levels of TNF-α following MBIs, an observation that was constant across different study protocols and populations [30]. Multiple studies also reported decreases of IL-6 following MBIs, although this effect might not be as generalized as TNF-α [30-34].

Despite a growing body of research highlighting MBIs' effects on inflammation, the underlying mechanisms are still poorly understood [35]. It is recognized that MBIs reduce depressive symptoms in different populations [36, 37], including the elderly [38, 39]. This is of interest since the expression of inflammatory markers, including IL-6, were found to be higher in depressed elderly patients with diabetes and co-occurring MCI in comparison to elderly diabetics with depressive symptoms, but without MCI [40].

Heightened levels of IL-6 and TNF-α have also been involved in the emergence of depressive symptoms in major depressive disorder [41-45]. Furthermore, a reduction in depressive symptoms has been observed following NSAIDs administration [46], as well as an attenuation of circulating inflammatory activation [47]. In light of the association between depressive symptoms and circulating cytokine levels, it is possible that the antidepressant effects of MBIs may be due, at least in part, to their normalizing effect on the inflammatory process. This hypothesis is particularly interesting to investigate in individuals with MCI because this population often presents co-occurring depressive symptoms, which in turn adds to the inflammatory burden associated to this prodromal phase [40]. This heightened inflammation could explain why MCI individuals with concomitant depressive symptoms are at a higher risk of developing AD than individuals with MCI without mood symptoms [48]. To our knowledge, the effects of a mindfulness

intervention on circulating levels of IL-6 and TNF-α has not yet been investigated in individuals with MCI.

1.1 Aims and Hypotheses

The primary objective of this study was to examine the effects of a MBI on plasma levels of pro-inflammatory cytokines of MCI participants, with a particular focus on TNF-α and IL-6 because they have been implicated in AD progression [13, 14]. Given the potential of MBI to decrease inflammation [30], it is hypothesized that lower levels of TNF-α and IL-6 will be observed in participants of the MBI group.

The secondary objective aimed to investigate the possible association between variations in cytokine levels and depressive symptomatology in participants who were administered a MBI. It is hypothesized that such associations will be observed given the strong relation between peripheral inflammation and depressive symptoms exposed earlier.

2. Materials and Methods

The study was approved by the Research Ethics Board of the *Centre intégré universitaire de santé et de services sociaux de la Capitale-Nationale* (CIUSSS-CN, approbation #2017-199) on August 21, 2017.

2.1 Participants

This study included 24 caucasian participants from both genders recruited through newspaper ads and medical references from Quebec City's (Quebec, Canada) physicians. Participants had to be at least 55 years old and meet the core clinical MCI criteria of Albert et al. (2011). All participants with MCI suffered at least a mild episodic memory impairment (with or without impairment in other cognitive domains). Consent and information forms were signed by all participants before the start of the study. The exclusion criteria were as follows: 1) history of moderate or severe traumatic head injury; 2) history of stroke; 3) delirium in the last 6 months; 4) history of encephalitis or bacterial meningitis; 5) history of psychotic symptoms or manic episode; 6) electroconvulsive therapy in the last 12 months; 7) history of intracranial surgery; 8) cancer treatment in the last 12 months; 9) general anesthesia in the last 6 months, 10) neurodegenerative disorders (except suspected prodromal manifestations of AD); 11) untreated medical or metabolic conditions; 12) current major depressive disorder according to the diagnostic criteria of the DMS-5 (APA, 2013); 13) current substance abuse; 14) uncorrected vision or hearing problems; 15) recent experience with psychotherapy or cognitive restructuring that might impact cognition; 16) significant experience with meditation or other contemplative approaches.

2.2 Screening Evaluation

Trained research assistants screened participants and collected pre- and post-test efficacy measures. Potential candidates first underwent a screening evaluation at the CERVO Brain Research Centre (Quebec, Canada). A personal history interview as well as clinical and neuropsychological questionnaires and tests were administered to determine eligibility to the

study. The presence of an objective cognitive impairment was verified based on local (when available) normative data for standardized neuropsychological tests.

Clinical and neuropsychological batteries at screening evaluation. The Montreal Cognitive Assessment (MoCA) [49, 50] provided an appreciation of global cognitive functioning whereas subjective cognitive complaints were assessed with the *Questionnaire de plainte cognitive* (Subjective Complaints Questionnaire) [51], which is a semi-structured interview to predict the patient's current ability in memory, orientation, language, activities and behavioural that relies on « yes » or « no » answers. Verbal episodic memory was evaluated with the *Test de rappel libre/rappel indicé à 16 items* (RL/RI-16 - 16-item Free and Cued Recall) [52, 53] and semantic memory was assessed with the Pyramids and Palm Trees Test [54, 55]. Both visuoconstructive abilities and visual episodic memory were assessed using the Rey-Osterrieth Complex Figure Test [56-58]. Visuo-perception was evaluated with the size match subtest of the Birmingham Object Recognition Battery [59], whereas the Coding subtest from the WAIS-III [60] served as a measure of information processing speed. As for language, confrontation naming was assessed with the 15-item Boston Naming Test [61], and phonemic and semantic fluency, with T-N-P and Animal fluency, respectively [62, 63]. The D-KEFS version of the Stroop [64] was chosen to evaluate executive functioning. Under the assumption that circulating levels of cytokines covary with cognitive [18] and psychological features [40], most tests were meant to establish group equivalence at baseline on such variables. Furthermore, some of those tests were relevant to confirm the diagnostic of MCI.

2.3 Interventions

The eligible participants were randomly assigned to one of the two study interventions. Each intervention group was composed of 12 participants and interventions were held over a period of 8 weeks, with weekly sessions lasting 2.5 hours, including a 15 minutes break mid-session (see Table 1).

Mindfulness-based intervention (MBI). The MBI was elaborated by Larouche, Chouinard, and Goulet [65]. The program was based on Kabat-Zinn's Mindfulness-Based Stress Reduction [29] and other sources [66-70]. The MBI was adapted to the needs and limitations of older adults with the help of recommendations from McBee [71] without compromising the essence and goals of leading mindfulness programs (ex: Mindfulness-Based Stress Reduction and Mindfulness-Based Cognitive Therapy). Adaptations included at-home meditative practices lasting 30 minutes rather than the usually recommended 40-45 minutes, execution of all forms of meditations in a seated position on a chair (with the exception of walking meditation), and simplified instructions with concrete examples relevant to the life of an aging person. Further information on the adaptations made to the standard MBI program can be found in Larouche, Chouinard, Morin-Alain, Hudon, & Goulet [72]. Group sessions comprised one or two guided meditation practices, group discussions, and psychoeducation about weekly mindfulness themes and stress management (see Table 1). Starting on week one, meditation practices were gradually introduced, starting with the body scan, mindful movements, meditation on senses (including mind sense), mindful walking, as well as mountains and loving-kindness meditations. Participants were also instructed to practice meditation at home for 30 minutes per day, six days a week, using vocal instructions on CDs, written instructions, as well as short texts related to weekly themes. In order to ensure adherence

or compliance to the intervention and to minimize attrition, participants were contacted by phone each week. The program was administered by its three developers, who possess the necessary credentials (available upon request).

Psychoeducation-based intervention (PBI). The PBI was developed by Parent, Larouche, Chouinard, and Hudon [73]. Participants were given psychoeducational classes on cognitive aging, each session being dedicated to a different topic (see Table 1). No reference was made to mindfulness techniques and attitudes or to strategies to improve cognition. A visually supported presentation was provided along with interactive activities consisting of group discussions, quizzes and smaller group interactions. Each participant received a binder with the written content of each session and room to take additional notes. The PBI was administered by Parent, who holds a master's degree in psychoeducation, and the first author of the present study.

2.4 Pre- and Post-Tests

At the pretest, one week before the beginning of the trial, blood samples were collected by a licensed nurse whereas questionnaires and tests were administered. Given the influence of certain nutrients [74] and circadian rhythm [75] on cytokine production, blood samples were collected between 7:00 and 9:00 AM while participants were fasting. A breakfast was then offered before collection of the remaining measures. One week after completion of their respective 8-week intervention program, all participants took part in the post-test with the same efficacy measures as the pretest.

Primary efficacy measures. Plasma concentrations of IL-6 and TNF-α were used to determine the effects of MBI and PBI on circulating inflammatory activation. Blood samples were collected in heparin tubes and centrifuged within the next 30 minutes for 15 minutes at 200g and 4 °C. The plasma was then aliquoted and stored at -80 °C until subsequent analyses. Plasma concentrations of IL-6 and TNF-α were analysed in triplicates using flow cytometry BD Biosciences Cytometric Bead Array (CBA) Human Enhanced Sensitivity Kit (Catalog No. 561521; Becton, Dickinson and Company; BD Biosciences, San Diego, CA, USA). A FACS Aria II cytometer and the FCAP Array software were used to analyse the samples according to the manufacturer's instructions (Becton, Dickinson and Company; BD Biosciences, San Diego, CA, USA). The sensitivity of the assay for each cytokine ranged from 274 to 200,000 fg/mL.

Secondary efficacy measure. Depression symptoms were determined with the full 30-item Geriatric Depression Scale, which demonstrates good reliability and validity (GDS) [76] and has been specifically validated with older adults with MCI [77]. A French version of the questionnaire was used [78]. For each of the 30 items, participants indicated whether or not the statement corresponded to how they felt in the last week. Of note, participants in this study did not meet diagnostic criteria of major depression according to the *Diagnostic and Statistical Manual of Mental Disorders-IV,* as evaluated with the Structured Interview for DSM disorders-I (SCID-1) [1, 79]. Depression symptoms, when present, were subclinical.

Moderator. Meditation practice at home was self-reported in a calendar. Participants noted the time they devoted to daily meditation as well as the type of meditation they practiced. This served to quantify adherence to the instructions and it allowed for assessment of the moderating effect of total practice time on plasma cytokine concentrations.

Table 1 Themes of MBI and PBI sessions.

	MBI	PBI
Session 1	Autopilot vs. mindfulness	Normal vs. pathological cognitive aging and myths on AD
Session 2	Handling obstacles and supporting meditation practice efforts	Memory functions and normal decline in aging
Session 3	Wandering mind	Dementia continuum and the frequency of mood symptoms
Session 4	Acknowledging stress and its impact of one's life to better manage it	AD risk factors and the influence of lifestyle habits on aging
Session 5	Reflecting on how one could live in increased acceptance of one's situation	Medical follow-ups and discussions with physicians about cognitive concerns
Session 6	The role thoughts play in the maintenance of distress and stress	Relationships and discussions about cognitive decline with close relatives
Session 7	How to take better care of oneself	Everyday living with cognitive decline and coping with difficulties
Session 8	Sustaining a meditation practice beyond the program	What to do next with all the new knowledge participants acquired in the program

Note. AD: Alzheimer disease; MBI: Mindfulness-based intervention; PBI: Psychoeducation-based intervention.

2.5 Statistical Analyses

Preliminary analyses. Data analyses were performed with the Statistical Package for the Social Sciences (SPSS, version 20) with a significance level set at $p < .05$. Variables were tested for normality of distribution, homogeneity of variance, and randomness of missing data distribution with the Shapiro-Wilk's, Levene's, and Little's Missing Completely at Random (MCAR) statistical tests. Pre-intervention group equivalence on sociodemographic and clinical variables was verified using Student's *t* tests for independent samples on continuous variables (i.e., education, Montreal Cognitive Assessment, and age) and a Chi-Square test for the nominal variable (i.e., sex). Since data relative to levels of cytokines were not normally distributed, Mann-Whitney U tests were used to achieve pre-intervention between group comparisons. Furthermore, Spearman correlations were calculated between levels of cytokines and the sociodemographic and clinical variables in order to add them as covariates in the subsequent mixed linear model, if necessary.

Efficacy analyses. A two factors (Intervention and Time) linear mixed model was carried out to determine differences between the two interventions groups (MBI and PBI) at the two-time repeated within group measures (pre- and post-intervention) for plasma levels of cytokines and scores on the GDS. For exploratory purposes and given the higher risk of AD progression with higher plasma levels of the two cytokines analysed [13, 14], each intervention group was split in

two based on baseline median plasma levels (0.08 pg/mL for TNF-α and 1.25 pg/mL for IL-6) to include this factor in the model. Cohen d's were used as indicators of interaction effect sizes [80, 81] and partial eta squares (ηp^2) were used as indicators of fixed factors' effect sizes [82]. Spearman correlations were calculated between scores' differences (deltas) for the two time points on the GDS and for the plasma levels of cytokines to determine potential relationships between cytokine changes and depression improvements resulting from the interventions.

Complementary analyses. To take into account the potential impact of meditation practice at home on the levels of cytokines post-intervention, MBI participants were divided into two subgroups according to the total amount of time dedicated to at-home meditation for the entire program (MBI+: total time above the median of 1.103 minutes; MBI-: total time below the median). As a comparative, the recommended time of at-home practice was equivalent to 1.440 minutes. These two groups were then compared for plasma levels of cytokines at pre- and post-intervention in a two-factor linear mixed model. Cohen's d and partial eta squares (ηp^2) were also calculated.

3. Results

3.1 Participants' Characteristics

Of the 24 participants included, 23 (11 in MBI and 12 in PBI) attended at least one intervention session and thus were included in the characteristic and correlation analysis for pre-intervention data. Of these 23 participants, 21 (9 in MBI and 12 in PBI) attended at least five sessions which is more than 50% of the total number of sessions and thus were included in the efficacy and complementary analyses following an "as treated" protocol [83]. Characteristics of participants on demographic and cognitive variables at pre-intervention are presented in Table 2, section A. Both interventions groups were equivalent on all variables, except for the second free recall on the verbal episodic memory test (RL/RI-16). Results for this second free recall on the RL/RI-16 were thus correlated to the efficacy measures at pre-intervention, IL-6 plasma levels (r_s [21] = -0.041, p = 0.854), TNF-α plasma levels (r_s [21] = -0.0231, p = 0.289) and scores on the GDS (r_s [21] = 0.425, p = 0.043). Only the latter was significant.

Table 2 Means (SD) and significance levels for all variables at pretest according to the intervention group.

A) Sociodemographic and cognitive variables.

Variables	MBI (n=11)	PBI (n=12)	*T value*	*df*	*P*
Sociodemographics					
Sex	5m/6f	7m/5f	0.38 (χ^2)	1	0.68[a]
Age	72 (5.37)	69 (6.23)	-1,10	21	0.28
Years of education	14 (4.06)	15 (2.16)	0.35	21	0.74
Global cognitive functioning and complaints					
Global cognitive functioning; MoCA (/30)	24 (2.86)	25 (1.00)	-0.55	21	0.59

Cognitive complaints; CCQ (/10)	6 (2.83)	5 (2.86)	-0.61	21	0.55
Verbal episodic memory; 16 word free and cued recall					
Free recall 1 (Z score)	-1.34 (0.84)	-0.64 (0.95)	1.87	21	0.08
Free recall 2 (Z score)	-1.69 (0.94)	-0.37 (1.00)	3.24	21	0.00*
Free recall 3 (Z score)	-1.47 (0.84)	-1.20 (0.69)	0.84	21	0.41
Delayed free recall (Z score)	-1.60 (1.15)	-1.17 (0.92)	0.98	21	0.34
Visual episodic memory; Rey figure copy task (immediate recall) (Z score)	0.47 (1.70)	-0.65 (2.02)	-1.42	21	0.17
Semantic memory; PPTT (% normal)	100%	100%	-	-	-
Verbal fluency					
Lexical (T-N-P task) (Z score)	-0.41 (0.85)	-0.55 (0.73)	-0.41	21	0.69
Semantic (Animal fluency) (Z score)	-0.30 (0.84)	-0.24 (1.02)	0.14	21	0.87
Confrontation naming (BNT, 15 items)					
Spontaneous (Z score)	0.10 (0.69)	-0.30 (0.88)	-1.20	21	0.25
Total (Z score)	0.25 (0.63)	-0.19 (0.79)	-1.47	21	0.16
Visuoperception and visuoconstruction					
Construction (Rey Figure copy) (Z score)	-0.63 (1.16)	-1.28 (1.18)	-1.34	21	0.19
Perception (BORB circles) (Z score)	-0.28 (0.97)	-0.54 (1.32)	-0.55	21	0.59
Executive functions (D-KEFS Stroop)					
Inhibition time (Z score)	-0.33 (1.20)	-0.14 (1.33)	0.37	21	0.72
Switching time (Z score)	0.17 (1.30)	-0.39 (1.39)	-0.96	20	0.35
Inhibition errors (Z score)	-0.09 (1.00)	0.20 (0.69)	0.80	21	0.43
Switching errors (Z score)	-0.23 (1.09)	-0.36 (0.99)	-0.28	20	0.78
Processing speed (Coding from WAIS-III) (Z score)	0.18 (0.87)	-0.09 (0.77)	-0.78	21	0.45

B) Primary and secondary efficacy measures.

Blood levels of cytokines (pg/mL)					
IL-6	2.56 (2.48)	2.92 (5.59)	-	-	0.260 (U)[b]
TNF-α	0.11 (0.10)	0.06 (0.05)	-	-	0.295 (U)[b]
Depressive symptoms					
GDS (/30)	10 (6.72)	8 (3.59)	0.95	21	0.36

Note. Result for plasma levels are in picograms per milliliter (pg/mL). PBI: Psychoeducation-based intervention, MBI: Mindfulness-based intervention; MoCA: Montreal Cognitive Assessment; BORB: Birmingham Object Recognition Battery; CCQ: Cognitive Complaint Questionnaire; D-KEFS: Delis-Kaplan Executive Function System; PPTT: Pyramids and Palm Trees Test; BNT: Boston Naming Test; WAIS: Weschler Adult Intelligence Scale. GDS: Geriatric Depression Scale; IL-6: Interleukin-6; TNF-α: Tumor Necrosis Factor Alpha; n: number of participants; SD= Standard deviation; p = significance level; df = degrees of freedom; m = males; f= females

a Significant level corresponding to Chi squared test

b Significant level corresponding to U Mann-Whitney test

*p <0.05

3.2 Preliminary Measures

Groups were equivalent at pre-intervention on primary and secondary efficacy measures (see Table 2, section B). Furthermore, there were no significant correlations between levels of cytokines at pre-intervention and the variables sex, age, education, and global cognitive functioning (see Table 3). One outlier in the PBI group was removed given the pronounced variation between post and pre-test levels (drop of 16.26 pg/mL), which differed from the rest of the group (Z=-3.16). As for TNF-α levels, 17.4% of the samples failed to reach acceptable detection range. After confirmation that these data were missing completely at random ($\chi 2 = 0{,}00$, $p = 1{,}00$), they were replaced with generated data below the detection range using the maximum likelihood model [84].

Table 3 Spearman correlations between demographic, clinical, and cognitive screening characteristics and blood levels of cytokines (pg/mL) for all participants at pre-intervention (N= 23).

	Age	**Years of education**	**Sex**	**MoCA (/30)**	**GDS (/30)**
IL-6	-0,062	-0,133	-0.236	-0,137	-0.073
TNF-α	0,005	-0,069	-0,098	0,096	-0,299

GDS: Geriatric Depression Scale; **MoCA:** Montreal Cognitive Assessment; **IL-6**: Interleukin-6; **TNF-α**: Tumor Necrosis Factor alpha

3.3 Primary Efficacy Measures; Plasma Levels of Cytokines

TNF-α. There was no overall effect of MBI or PBI on plasma levels of TNF-α (see Figure 1).

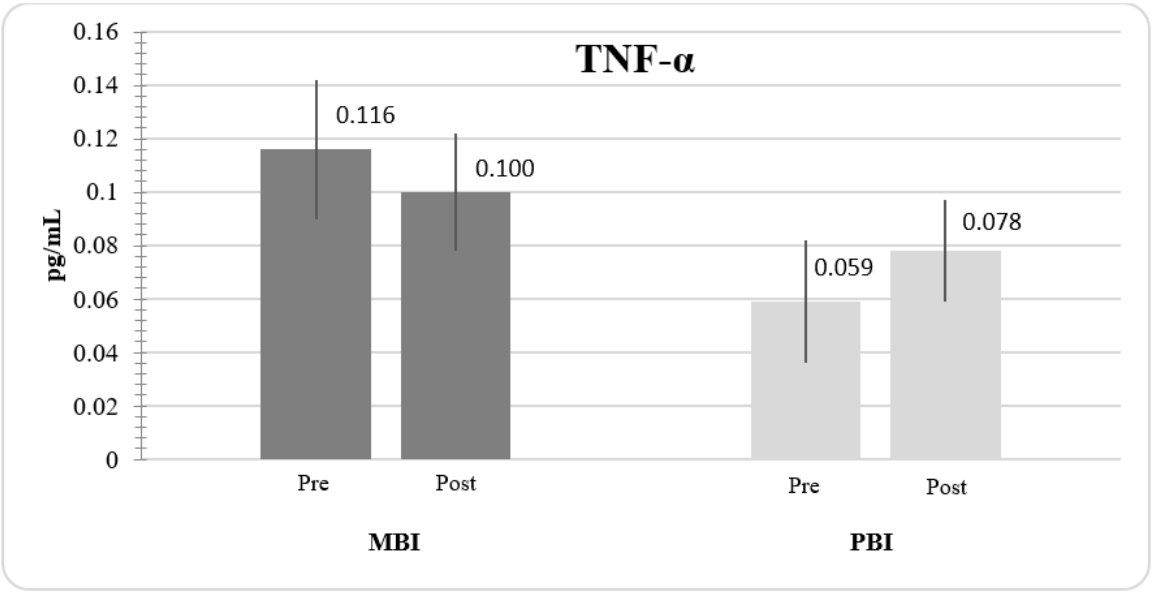

Figure 1 Plasma levels (pg/mL) of TNF-α in MBI (n= 9) and PBI (n= 12) groups at pre- and post-test**. Pre**: pretest; **Post**: post-test; **MBI**: Mindfulness-based intervention; **PBI**: Psychoeducation-based intervention; **pg/mL**: Picogram per milliliter.

The Time (p = 0.890, η_p^2 =0.00) and Intervention (p = 0.204, η_p^2 = 0.083) factors as well as the Time x Intervention interaction (p = 0.127, d = 0.036) were not significant. However, when each of the intervention group was divided according to baseline levels of TNF-α, visual inspection of Figure 2 suggested that MBI participants with higher initial levels of TNF-α had reduced levels of this cytokine after the intervention. The use of a three-factor linear mixed model confirmed that the Time, Intervention, and Initial plasma level interaction was not statistically significant (p = 0.252) but was coupled with a moderate effect size (d = 0.622). Pairwise comparisons showed that plasma TNF-α levels did not significantly change between the two time measures for the MBI-low initial level group (p = 0.330), the PBI-low initial level group (p = 0.168), or the PBI-High initial level group (p = 0.682) and that a non-significant trend for the cytokine to decrease in the MBI-High initial level group was observed (MBI-High; p = 0.068). This tendency was coupled with a moderate effect size (d = 0.500) as compared to the MBI group as a whole (d = 0.195).

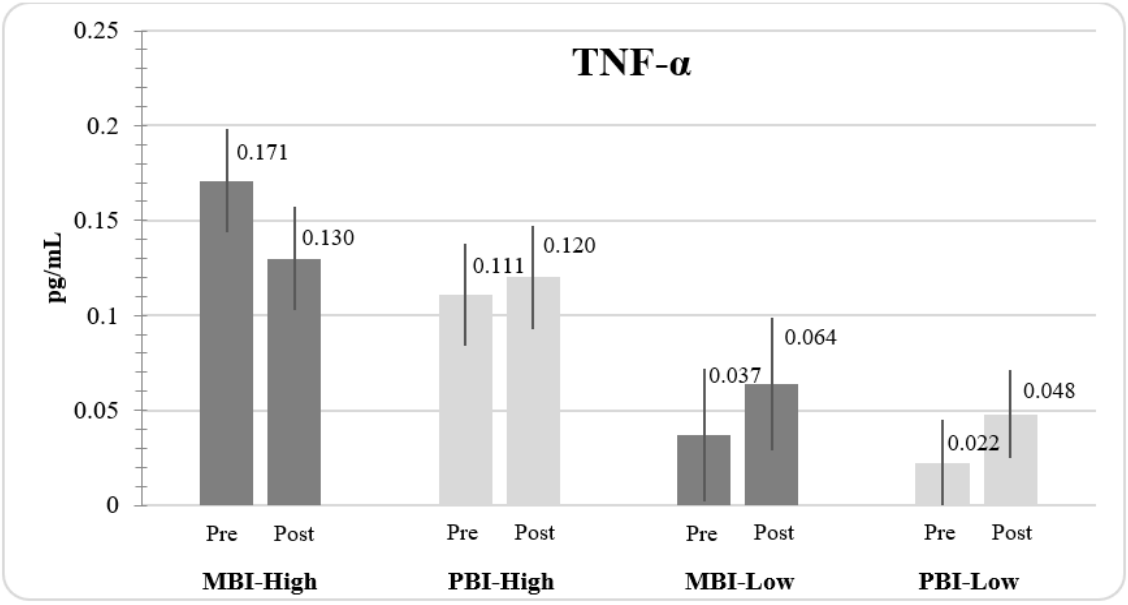

Figure 2 Plasma levels (pg/mL) of TNF-α in MBI (n = 9, high = 5, low = 4) and PBI (n = 12, high = 4, low = 8) groups at pre- and post-test according to initial levels**. Pre:** pretest; **Post**: post-test; **MBI-High**: Mindfulness-based intervention, high initial plasma level; **MBI-Low**: Mindfulness-based intervention, low initial plasma level; **PBI-High**: Psychoeducation-based intervention, high initial plasma level; **PBI-Low**: Psychoeducation-based intervention, low initial level **pg/mL**: Picogram per milliliter.

IL-6. Visually, IL-6 plasma levels seemed to increase in the MBI group following the intervention, whereas levels in the PBI group did not appear to differ from the pretest to post-test (see Figure 3).

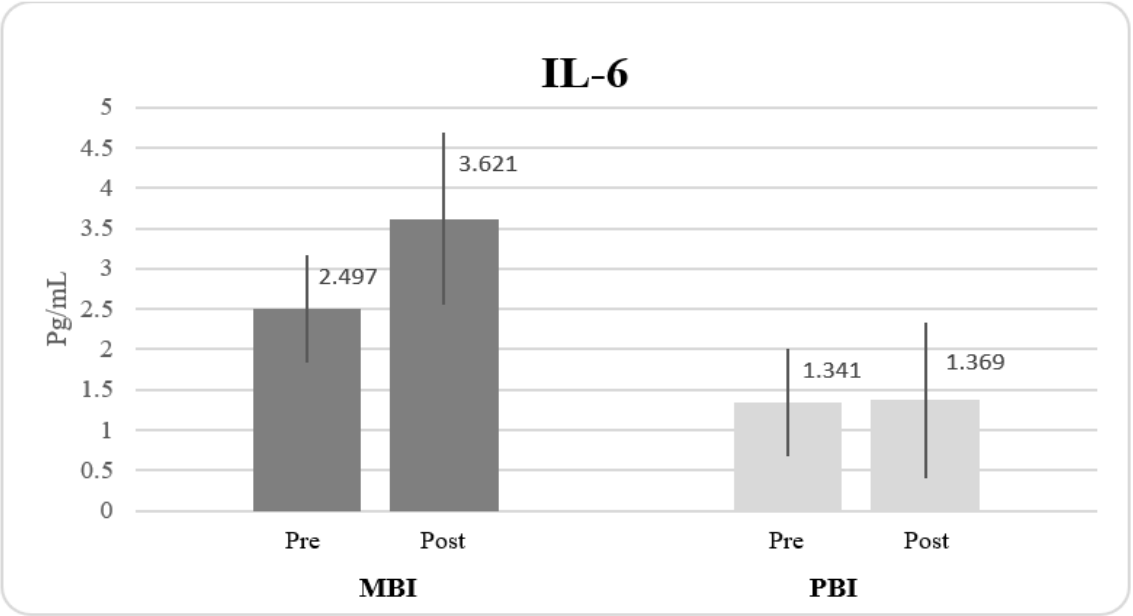

Figure 3 Plasma levels (pg/mL) of IL-6 in MBI (n = 9) and PBI (n = 11) groups at pre- and post-test. **Pre**: pretest; **Post**: post-test; **MBI**: Mindfulness-based intervention; **PBI**: Psychoeducation-based intervention; **pg/mL**: Picogram per milliliter.

The factors Time (p = 0.110, η_p^2 = 0.135) and Intervention (p = 0.157, η_p^2= 0.108) were not significant. Likewise, the Time x Intervention interaction was not significant (p=0.128) but was associated with a moderate effect size (d=0.54). Pairwise comparisons revealed a significant increase of plasma IL-6 levels from pretest to post-test in the MBI group (p = 0.04), with no significant cytokine variation in the PBI group (p = 0.952). The split of participants according to plasma IL-6 levels at pre-intervention did not yield a significant Time, Intervention, and Initial plasma level interaction (p = 0.884, d = 0.351) (see Figure 4). No particular tendency worthy of further analyses was observed on the basis of this categorization.

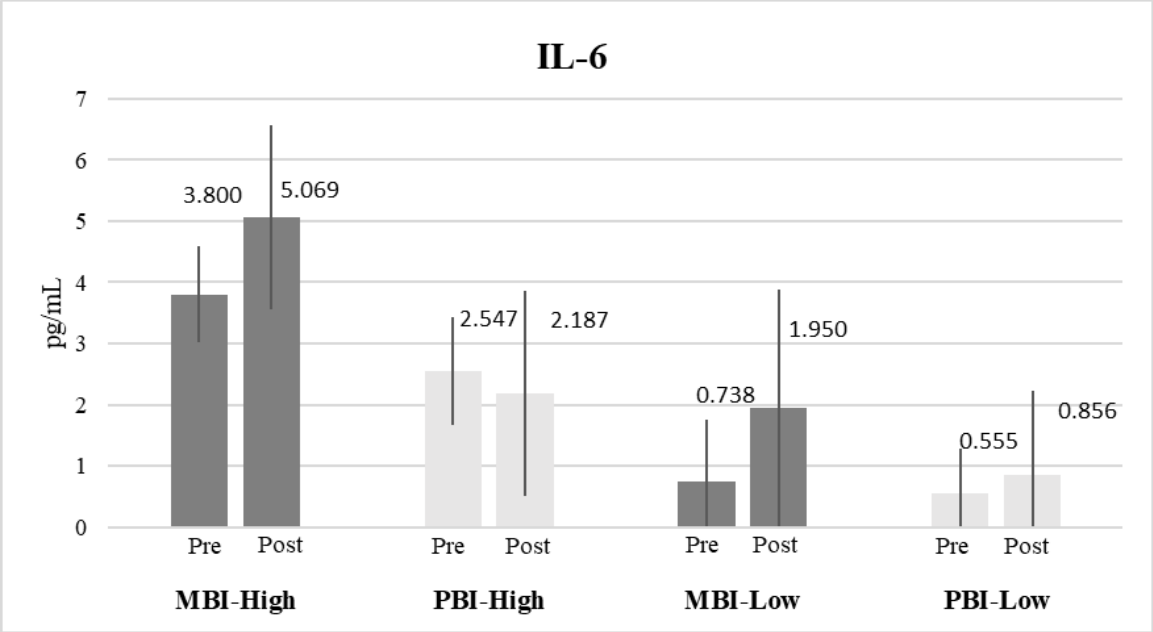

Figure 4 Plasma levels (pg/mL) of IL-6 in MBI (n = 8, high = 5, low = 3) and PBI (n = 10, high = 4, low = 6) groups at pre- and post-test according to initial levels**. Pre:** pretest; **Post**: post-test; **MBI-High**: Mindfulness-based intervention, high initial plasma level; **MBI-Low**: Mindfulness-based intervention, low initial plasma level; **PBI-High**: Psychoeducation-based intervention, high initial plasma level; **PBI-Low**: Psychoeducation-based intervention, low initial level **pg/mL**: Picogram per milliliter.

3.4 Secondary Efficacy Measures; Depressive Symptoms

Following each intervention, GDS scores decreased on average by about two points. The mean score in the MBI group went from 11.3 ± 1.7 to 9.8 ± 2.1 and from 7.8 ± 1.5 to 5.1 ± 1.8 in the PBI group. However, the Time (p = 0.09, η_p^2 = 0.144) and Intervention (p = 0.548, η_p^2 = 0.150) factors were not statistically significant, and no Time x Intervention interaction was found (p = 0.626, d = 0.224). GDS scores were not correlated with either IL-6 (r_s [21] = -0.073, p= 0.741) or TNF-α (r_s [21] = -0.299, p = 0.165) levels at pre-intervention. No significant correlations were obtained between GDS score differences (deltas) at the two measure points and the levels of IL-6 (r_s [18] = 0.130, p = 0.586) and TNF-α (r_s [19] = -0.138, p = 0.550).

3.5 Complementary Measures; Amount of Meditation Practice

Effect on TNF-α levels. No significant effect of meditation practice on TNF-α was observed in MBI participants, although a non-significant trend towards a decrease in TNF-α levels at post-intervention was observed in participants with a higher meditative practice (*d*= 0.405), with no effect noted for participants who practiced less (*d*= 0.066) (see Figure 5). The effect of Time alone on TNF-α levels was not significant (p = 0.425, η_p^2 = 0.101) and no significant Time by Amount of meditation practice interaction was observed (p = 0.280), but the effect size was moderate (*d*= -0.471).

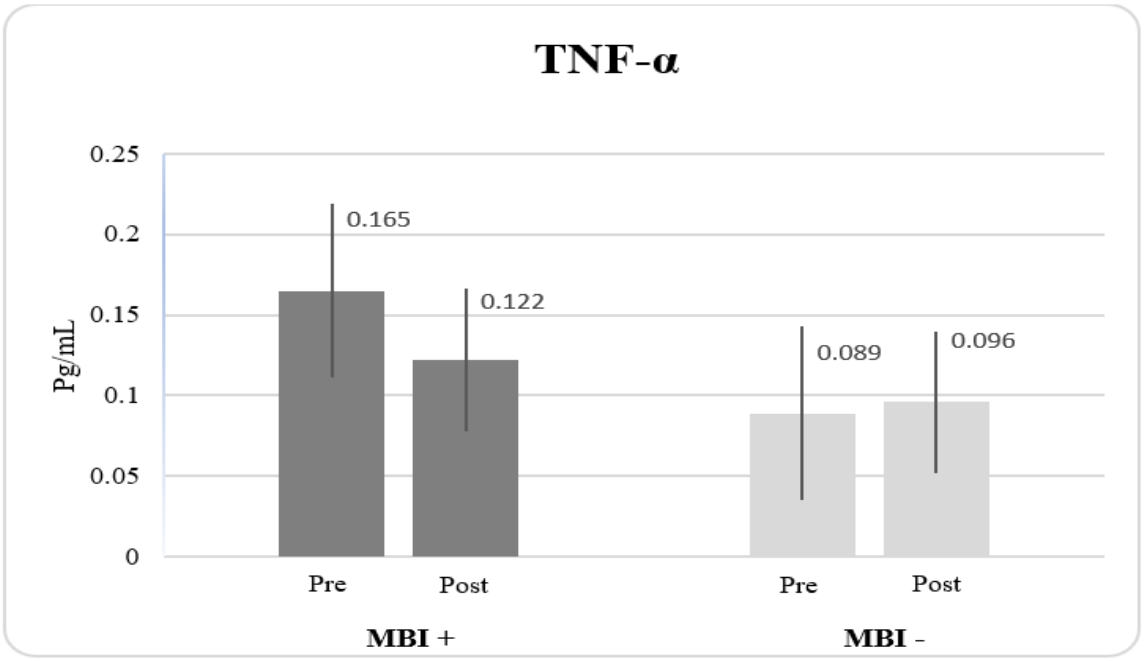

Figure 5 Plasma levels of TNF-α at pre and post-test for MBI participants according to amount of meditation practice. **MBI +**: Above median meditation practice subgroup (n= 4); **MBI**-: Below median meditation practice subgroup (n= 4).

Effect on IL-6 levels. A non-significant trend towards an increase in IL-6 levels post-MBI was more marked for participants who devoted more time to meditation practice relative to those who meditated below the median. Indeed, IL-6 concentrations of individuals with a higher meditation practice increased by 1.710 pg/mL ± 0.880, *d*= 0.631, whereas IL-6 concentrations of individuals with a lower meditation practice increased by 0.784 pg/mL ± 0.880, *d*= 0.377. The factor Time was not significant (p = 0.206, η_p^2 = 0.251). The Time x Meditation practice interaction was not significant either (p= 0.618), and the effect size was low to moderate (*d* = 0.254).

4. Discussion

The primary objective of this study was to examine the effects of MBI on circulating levels of pro-inflammatory cytokines of MCI participants, with a particular focus on plasma levels of TNF-α and IL-6. As a secondary objective, the study aimed at investigating the possible associations between variations in cytokine levels and depressive symptomatology in the MBI group, which

could have been suggestive of inflammatory-driven mechanisms leading to mood improvements in these participants.

Although no robust effects of the study interventions on plasma levels of pro-inflammatory cytokines were observed, some observations appeared to be in line with a priori hypotheses and previous literature. In particular, TNF-α levels tended to decrease post-MBI but only in participants who had higher levels of the cytokine before the intervention, suggesting that mindfulness interventions could be more impactful in individuals with higher baseline inflammatory states. This was specific to MBI since PBI participants did not show such a tendency. Interestingly, TNF-α levels also tended to decrease in those participants who practice more meditation at home, an aspect that future studies should investigate. This inclination towards a decrease in TNF-α for the MBI group is consistent with previous findings. Mindfulness interventions have been associated with decreased circulating levels of TNF-α, an effect that was generalised across study designs (population of interest, type of mindfulness practice, study protocol, etc.) [30]. In line with the view that mindfulness effect could be dependent on the initial inflammatory state of the body, antidepressant effects of infliximab, a TNF-α antagonist drug, were only observed in participants with higher initial level of TNF-α [85]. Alternatively, in this study, the trend towards decrease of TNF-α levels following MBI could be due to the fact that several MCI participants were actually in the prodromal phase of AD. Indeed, as mentioned earlier, higher circulating levels of TNF-α, as compared to healthy controls, were associated with a higher risk of progression from MCI to AD [86]. Some authors listed TNF-α amongst the most predictive biomarkers of AD [87]. Longitudinal studies will be necessary to explore the hypothesis of a decrease in TNF-α specific to MCI individuals having higher initial levels of this cytokine, and thus being at higher risk of developing AD.

In contrast with our initial hypotheses, a trend towards heightened plasma IL-6 was observed post-MBI, which appeared to be more pronounced in participants who devoted a higher amount of meditation practice at home. Unlike TNF-α that displays consistent patterns following mindfulness interventions, literature reviews and meta-analysis did not report overall decreases or increases for IL-6 following mindfulness interventions, which could be due to this cytokine's sensitivity to variations in clinical trial characteristics (study protocol, population studied, etc.). Nevertheless, some studies did report a rise of IL-6 following mindfulness interventions in populations such as breast cancer patients [88] and healthy adults [89], and this rise was considered beneficial. In the context of AD, however, the overall assumption regarding peripheral levels of IL-6 is that of a gradual augmentation with the progression of the disease [13, 90]. The specific role of IL-6 in AD has yet to be determined, but it has been suggested that its secretion could contribute to a damageable pro-inflammatory response involved in AD pathogenesis [11]. In this frameset, an intervention that increases levels of IL-6 in MCI participants could thus be considered detrimental. However, the evolution of IL-6 in AD could be more complex and sensitive to the progression of the disease over time. A multicentre study carried out by Cao and collaborators [91] revealed lower plasma levels for this cytokine in MCI participants who later progressed to MA within two to four years compared to participants who remained stable, suggesting that a failure of the immune system to generate an appropriate response at a crucial time could promote the installation of AD pathology. In line with this view, the longitudinal PREVENT-AD study reported the decrease of six cerebrospinal fluid inflammatory markers with the first signs of Aβ and Tau pathology, followed by a strong sustainable increase [92], adding support

to the hypothesis of an impaired inflammatory response in the early stages of AD favouring the evolution of the pathology. Similarly, an inverse association between chronically raised C reactive protein (a pro-inflammatory mediator) and cerebral amyloid beta (Aβ) has been reported in non-demented elderly individuals reporting subjective memory complaints [93], suggesting that certain inflammatory processes could be beneficial at early stages of AD as the immune system attempts to combat Aβ pathology. According to this hypothesis, a strong immune response might be necessary for defending the brain and body against the formation of Aβ plaques and other pathophysiological processes in the early stages of AD. Therefore, the trend towards an increment in IL-6 following MBI observed in this study, although nonsignificant could indicate a useful pro-inflammatory response since its timing is opportune (MCI stage), a hypothesis that should be addressed in longitudinal studies.

Contrary to our hypothesis, plasma cytokine changes in the MBI group, although non-significant, were not associated with variations in depressive symptomatology. Depressive symptomatology is dependent on a plethora of environmental factors. There is a lot of heterogeneity between participants in this regard. In our understanding, an elevated level of circulating cytokines is not causative of the depressive symptomatology but covary with it and contributes in the perpetuation of those symptoms. A larger study is necessary to explore this association. With authors reporting an association between stress reduction and inflammation variations following a compassion meditation practice [94], this possible association was also briefly investigated in this study. Indeed, this project being embedded in a larger one, we were able to conduct exploratory analysis with perceived anxiety symptoms of participants using the GAI (Geriatric Anxiety Inventory). For methodology on this matter see Chouinard, Larouche, Audet, Hudon, & Goulet [95]. No significant association was found between the GAI scores and IL-6 (r_s [21] = -0.089, p= 0.685) or TNF-α (r_s [21] = -0.262, p= 0.227) levels at pretest. Also, no significant correlations were found between score differences at the two measure points of the GAI and the levels of IL-6 (r_s [18] = -0.067, p= 0.780) and TNF-α (r_s [19] = -0.074, p= 0.750). This absence of associations between variations of psychological and cytokine measures might indicate that the effect of mindfulness on both of these outcomes does not stem from a common action mechanism, but rather from independent ones. It is also possible that the variation on depressive symptoms was not important enough to correlate with other pre-post variations in cytokine plasma levels. Participants had mild depressive symptoms [96] on average pre-intervention. Although there was a decrease towards a normal range of symptoms post-intervention in both groups, the decrease was not statistically significant. Perhaps a more severe depressive symptomatology at baseline would have been more favorable statistically, but this is not what the present sampling method yielded. As well, groups differed on the second free recall of the RL/RI-16, which positively correlated to GDS scores. This could have exerted an influence on the results, although this positive correlation is surprising given that depressive symptoms usually have a negative influence on memory performances, especially in the elderly [97]. One other explanation could be that the initial levels of TNF-α were not high enough to observe a diminution in depressive symptomatology, as was observed in the infliximab trial by Raison and collaborators [85]. Further studies are necessary to test these hypotheses, with a larger sample size to conduct moderation analysis, a more robust design to investigate the complex relations between physiological and psychological measures.

This study has limitations. First, due to its exploratory nature, the number of participants was limited. Nevertheless, the tendencies observed, although they did not reach significance, could

guide future research on the physiological effects of mindfulness interventions. Second, the loss of TNF-α data calls for caution regarding the interpretations of the variation of this cytokine following the MBI and PBI. Although the present results are interpreted in light of an active control group with participants having similar neuropsychological, clinical, demographic, and physiological profiles at pre-intervention, thus controlling for a number of confounding variables, further studies must be conducted to confirm the tendencies observed. Nevertheless, the use of the PBI group has permitted the distinction of tendencies specific to the MBI, such as the trends towards IL-6 elevations and TNF-α reductions that were only observed for this intervention. Furthermore, there are possible meditation practice effects associated with both cytokines, which could further reinforce the notion of a MBI-specific effect on inflammation profiles in participants with MCI.

5. Conclusions

To our knowledge, this is the first study to investigate the effects of a MBI compared to an active control condition on the circulating inflammatory levels of pro-inflammatory cytokines in participants with MCI. These preliminary findings suggest tendencies for plasma levels of IL-6 and TNF-α that were specific to MBI. This is of importance since both cytokines have known implications in the pathophysiology of AD. Therefore, interventions that could modify the peripheral inflammation profile of people at risk for AD could potentially limit or alter the progression of the disease. MBIs show promise since they are easily implemented, affordable, and may have beneficial physiological effects on modifiable risk factors of AD.

This exploratory study opens the way to further investigations regarding this preventive strategy. Future studies might want to include a more sensitive detection kit and a larger sample of participants in order to replicate these results with more certainty. Furthermore, additional participants would allow for moderation analysis, which would permit further investigation of the action mechanism behind MBIs. Finally, given the interesting variations on cytokine levels with the progression of AD, a longitudinal study could be interesting to assess the long-term effects of MBIs on inflammatory markers of elderly with MCI, especially in relation to the evolution of their condition.

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Author Contributions

Valérie Morin-Alain contributed to the elaboration of research questions, literature review, recruitment and data collection, administration of the PBI, data entry, analysis and interpretations and the writing of the article.

Eddy Larouche contributed to the elaboration of the study protocol, recruitment and data collection, analysis, creation of both intervention manuals and administration of the MBI.

Anne-Marie Chouinard contributed to the elaboration of the study protocol, recruitment and data collection and creation of both intervention manuals.

Marie-Claude Audet supervised the scientific methods behind the obtention of the physiological data and contributed to the interpretations of results and the writing of the article.

Sonia Goulet contributed to the supervision of the scientific method, elaboration of the study protocol, creation of intervention manual and administration of the MBI, results interpretations and writing of the article.

Louis-Simon Rousseau contributed to the interpretations of results and the writing of the article.

Carol Hudon contributed to the supervision of the scientific method, elaboration of the study protocol, results interpretations and writing of the article.

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Competing Interests

The authors have declared that no competing interests exist.

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