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Changes in hair cortisol and self-reported stress measures following mindfulness-based stress reduction (MBSR): A proof-of-concept study in pediatric hematology-oncology professionals

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Lists of abbreviations

MBSR	Mindfulness-Based Stress Reduction
HCC	Hair Cortisol Concentrations
PSS	Perceived Stress Scale
BSI	Brief Symptom Inventory
MBI-SS	Maslach Burnout Inventory Student Survey
MBI	Maslach Burnout Inventory
HPA	Hypothalamic-Pituitary-Adrenal
CRH	Corticotropin-releasing hormone
ACTH	Adrenocorticotropic hormone
UHC	University Health Center

ABSTRACT

Background and purpose. Little data is available on the effect of mindfulness amongst pediatric hematology-oncology professionals. The purpose was to further document change in biological and psychological stress following a mindfulness-based stress reduction (MBSR) program.

Materials and methods. We led two pre-post interventional studies (n = 12 and n = 25) and measured changes on hair cortisol concentrations, perceived stress, psychological distress and burnout.

Results. Professionals did not change on biological stress (d = 0.04), but improved on self-reported measures (median d = 0.58). Effects were maintained over 3 months for psychological distress, anxiety, depression, and burnout (median d = 0.66). Effects were larger if trainees participated to the retreat and if they reported higher baseline perceived stress.

Conclusion. In pediatric hematology-oncology professionals, an MBSR program was related with improvements in self-reported stress over 3 months. Components of the program and characteristics of trainees may influence the impact of MBSR.

Keywords: burnout; cortisol; hematology-oncology; mindfulness-based stress reduction; professional caregivers; stress

1. INTRODUCTION

Healthcare professionals (HCPs) working in hematology-oncology face chronic stress and exhaustion, which can affect their health, quality of life, and job performance [1]. In pediatric hematology-oncology specifically, professionals face unique stressors, including treatment complexity, ethical and moral dilemmas, support for children and families, child suffering, loss, and bereavement [1-3]. A worldwide survey of 1,047 pediatric oncologists has indicated that 38% reported high levels of burnout [2]. Given the high prevalence of chronic stress among pediatric hematology-oncology HCPs, and its consequences both on professionals and their patients, interventions aimed at reducing stress and preventing burnout are essential.

Prolonged chronic stress manifests itself cognitively, emotionally, behaviorally, and in the body itself. When the stress response becomes chronic, harmful effects on the body are evidenced over time [4,5]. Chronic stress is typically reflected by prolonged secretion of cortisol which has been linked to anxiety and depression, hypertension, obesity, metabolic-syndrome, type 2 diabetes, cardiovascular disease, and sleep difficulties [6-8].

Mind-body interventions including mindfulness practice can help HCPs cope with stressors [9]. Mindfulness, which has its origins in Buddhism, has been described as "paying attention in a particular way: on purpose, in the present moment, and nonjudgmentally" [10]. The Mindfulness-based stress reduction (MBSR) program has been shown to reduce perceived stress, anxiety and depression, psychological distress and burnout, and to improve empathy and positive affects in professional caregivers [11-14]. To date, only one study has investigated the impact of MBSR in pediatric hematology-

oncology [15]. In a randomized trial involving 48 HCPs (mostly nurses), authors did not find any significant quantitative improvements in self-reported perceived stress, depression or burnout. Yet, researchers qualitatively reported improvements in stress, inner peace, joy, compassion, focus, self-awareness and somatic symptoms in the intervention group, supporting further studies in this population. Importantly, the intervention was not a standard MBSR course and fidelity to the program was not documented.

Recent results suggest that participating in an MBSR program is associated with a decrease in cortisol levels [16-19], although the result is not fully consistent in the literature [20-22]. Most studies have measured levels of cortisol in samples such as blood or saliva, which only allows for short-term assessments of this biomarker [23]. A relatively new strategy for measuring chronic stress is the analysis of hair cortisol concentration (HCC) [24]. This method allows a retrospective measurement of the secretion of cortisol over longer periods of time and a potentially suitable approach to chronic stress [25]. A recent comprehensive meta-analysis has indicated that populations exposed to chronic stress show a 22% increase in HCC. This increase is even greater (43%) when stressors are still present at the time of the study [23]. To date, only one study examined the impact of MBSR on cortisol levels (salivary) in HCPs and found no change on this outcome [21]. Notably, no studies have measured the effect of an MBSR program on HCC.

To address these gaps in the literature, we conducted two successive studies. Study 1 was performed to test procedures in a small convenience sample of students. We wished to test the detailed collection of outcomes in relation with the MBSR program. Study 2 was a replica of Study 1 in the targeted population, i.e. pediatric hematology-

oncology HCPs, with the addition of a follow-up. Since the same intervention and the same outcomes were evaluated in both studies, we give results for both groups.

We had two aims: 1) To assess if participation in an 8-week MBSR program was related to improvements in biological stress and psychological stress. 2) To explore if changes over time from Aim 1 would be moderated by participation intensity and baseline stress.

2. MATERIALS AND METHODS

2.1. Design

Following current guidelines when using newly developed outcomes in a rarely studied population, we performed pretest-posttest Phase IIa proof-of-concept studies focusing on identifying the size of change on outcomes or interest [26]. The feasibility of the current program was analyzed in a previous report [27]. Thus, the present report focuses on the size of change in targeted outcomes. As the procedure-testing in Study 1 was largely positive [27], we decided to report changes from both Studies 1 and 2 and not just the target HCPs sample, as planned initially. Measures were taken pre and post for both studies, and a 3-month follow-up was added for Study 2.

2.2. Participants and procedures

Study 1 took place between October 2015 and March 2016 at the University of Montreal with university psychology students; Study 2 took place at the Sainte-Justine UHC (Montreal, Canada) from March to May 2016 with HCPs from a pediatric hematology-oncology department. Inclusion criteria for both studies followed guidelines

outlined by the creators of MBSR [28]: a) comprehension of the language in which the program is offered (in this case French); b) the ability to comply with the requirements of the program; c) no previous participation in a MBSR program; d) no clinical depression or other major psychiatric diagnosis; e) no active substance dependence; f) no psychotic symptoms; g) no suicidality. Screening for eligibility was performed in an initial individual interview with the instructor (ML). Information was given and all participants completed an informed consent during this encounter. The research was approved by the research ethics committee of the hospital and the university (#2016-1068). In Study 1, undergraduate and graduate students of the University of Montreal Psychology Department (n = 1,130) were approached by email to participate in an 8-week MBSR program. In Study 2, dayshift HCPs working in the hematology-oncology department of our hospital (n = 109) were approached via emails and posters to attend an information session about an 8-week MBSR program. This approach was preceded by two buy-in meetings.

2.3. Intervention

The intervention was based on the mindfulness-based stress reduction program (MBSR) [29], consisting of eight weekly 2-hour sessions and a one-day silent retreat between sessions 6 and 7. During the sessions, participants were trained in four techniques of formal meditation (body scan, sitting meditation, walking meditation, and mindful yoga), and informal meditation practice (practicing mindfulness in daily activities). They practiced at home with the help of a workbook and audio recordings (transcripts of guided meditations created for the program available in French and

English [27]). An instructor trained in MBSR at the University of Massachusetts Medical School (ML) guided the sessions and the silent retreat. To ascertain treatment fidelity, sessions with the target group of HCPs (Study 2) were videotaped for supervision by a certified MBSR instructor with extensive experience (PD, see Acknowledgments).

2.4. Measures

Hair cortisol and self-report measures were taken at three time-points: pre-intervention (Studies 1 and 2), 3 months later (one month after the intervention, Studies 1 and 2), and again 3 months later for follow-up (Study 2 only).

2.4.1. Hair cortisol concentrations (HCC)

We used the analysis of HCC to evaluate levels of chronic stress in participants. HCC, reported in picograms per milligram (pg/mg), are a recent way to measure cumulative cortisol levels in hair using enzyme immunoassays. Since cortisol levels accumulate in hair, and hair grows an average of 1 cm per month, the analysis of 3 cm of hair can be used to assess cumulative exposure to stress within the last 3 months. Recent findings indicate the overall validity of HCC to assess cortisol levels over a long period of time, as well as its test-retest reliability and acute/situational stability [23]. Samples can be easily collected and stored at room temperature without storage equipment [24].

For each participant in both studies, a research assistant collected a small lock of hair (about 0.5 cm thick and 1 cm wide) closest to the scalp, about 4 cm above the skull base. We also asked participants about their hair history because washing, dyeing, and hair products might affect hair cortisol concentrations [23]. Before being analyzed, hair samples were stored in sealed plastic bags identified with participants' IDs, in the dark, and at room temperature. Analyses were performed at the Center for Studies on Human

Stress BioAssay Lab in Montreal using an ELISA platform (University of Montreal, Dr. Sonia Lupien, https://humanstress.ca).

2.4.2. Perceived stress

Perceived stress was assessed using the Perceived Stress Scale (PSS-10) [30], a validated 10-item questionnaire measuring perceived stress on a 5-point Likert scale ranging from 0 (never) to 4 (very often). A sample item is: "In the last month, how often have you been able to control irritations in your life?". Internal reliability coefficients in the samples were excellent (Study 1: α = 0.88, Study 2: α = 0.83). Perceived stress, as well as all the following self-report measures, were collected as part of questionnaires completed online on the SurveyMonkey® platform.

2.4.3. Psychological distress

This was measured with the Brief Symptom Inventory-18 (BSI-18) [31], an 18-item self-reported questionnaire answered on a 5-point Likert scale (0 = not at all, 4 = extremely). The questionnaire comprises a total score, the General Severity Index (GSI), and three 6-item dimensions: anxiety, depression, and somatization. Examples of items include: "Nervousness or shakiness inside" (anxiety), "Feeling of worthlessness" (depression), and "Faintness or dizziness" (somatization). Caseness for distress was determined according to the algorithm available in the manual [32]. Internal reliability coefficients were satisfactory in both studies on distress (α = 0.83; 0.90), anxiety (α = 0.70; 0.82), depression (α = 0.82; 0.85), and somatization (α = 0.72; 0.67).

2.4.4. Burnout

For Study 1, burnout was measured using a version of the Maslach Burnout Inventory (MBI) designed for students, the MBI-Student Survey (MBI-SS) [33]. The MBI-

SS contains 15 items scored on a 7-point Likert scale (0 = not at all/never, 6 = very well/often). The questionnaire is divided into three subscales: exhaustion (5 items), cynicism (4 items), and efficacy (6 items). An example of an item of the MBI-SS is: "I feel used up at the end of the day at school". For Study 2, we used the Maslach Burnout Inventory (MBI) [34], a 22-item questionnaire scored on a 7-point Likert that assesses emotional exhaustion (9 items), depersonalization (5 items), and personal accomplishment (8 items). An example of an item is: "Working with people directly puts too much stress on me". For Study 1, the burnout levels high, moderate, and low, are based on reported cut-points [35]. For Study 2, burnout levels categories are based on norms for nurses and physicians reported in the MBI manual [36]. Low consistency was observed in cynicism (Study 1, $\alpha = 0.33$) and personal accomplishment (Study 2, $\alpha = 0.49$), so results involving these measures should be interpreted with caution. Other scores had satisfactory internal consistency: exhaustion (Study 1, $\alpha = 0.83$), emotional exhaustion (Study 2, $\alpha = 0.77$), depersonalization (Study 2, $\alpha = 0.67$), and efficacy (Study 1, $\alpha = 0.66$).

2.4.5. Practice

We evaluated the intensity of practice at home with two items: (1) estimated number of hours of formal home practice recorded by the participants, such as yoga, meditation, body scan, walking meditation; (2) estimated number of hours of informal home practice, such as being mindful while performing daily tasks like cooking. In addition, we recorded participant's presence to each invidual session, including the silent retreat.

2.5. Statistical analysis

For Aim 1, we performed Student's *t* tests to compare pre/post differences in Study 1. In Study 2, we performed a linear mixed model for repeated meesures over time to analyze the impact of the program at post-intervention and follow-up with fixed effects of time, using maximum likelihood (ML) estimation. This method prevented listwise deletion due to missing data. We also performed McNemar's tests in both studies to test for significant change in proportions over time in the number of cases showing high levels of distress and burnout. For Aim 2, we used Pearson's correlations to evaluate associations between changes on different outcomes and potential moderators. In line with the objective of a proof-of concept study, we emphasize effect sizes (*d* and *r*) [26]. In hypothesis testing, we used an alpha value of 0.05. Statistical analyses were performed with IBM SPSS Statistics version 24.0 (IBM Corp., Armonk, N.Y., USA).

3. RESULTS

Fig. 1 shows the flow of participants of both studies. In Study 1, 43 students were interested in taking part in the study. The first 16 participated in an interview and were assessed for eligibility. Fifteen were finally enrolled in the study. Of these, 12/15 (80 %) completed at least 6 sessions (retention rate = 80%). Moreover, 15/15 (100%) completed the pre-intervention survey, 12/15 (80%) completed the post-intervention survey, and 11/12 (92%) attended the silent retreat. Three students (20%) withdrew from the program (two students following the first session for personal reasons and one after the fourth session for time conflict). The final sample for analyses consisted of 12 students. Eleven (92%) were female.

In Study 2, 41/109 (38%) eligible HCPs showed interest in taking part in the study. Among these, 28/41 (68%) were recruited to participate in the study; 2/28 (7%)

left before the beginning of the program due to scheduling conflicts. Therefore, 26 HCPs were enrolled in the program (Fig. 1). One participant (4%) withdrew from the program after two sessions due to scheduling conflict. 21/26 participants completed at least six sessions, yielding to a retention rate of 81%. Twenty-six participants (100%) completed the pre-intervention survey, 25/26 (96%) completed the post-intervention survey, 24/26 (92%) completed the follow-up survey, and 19/26 (73 %) attended the one-day silent retreat. Twenty-two (88 %) were female (Table 1). The home formal practice (body scan, meditation, yoga) for the 8-week program was on average 9.8 hours for Study 1 and 24.9 hours for Study 2. The home informal practice was on average 2.5 hours for Study 1 and 11.4 hours for Study 2. Additional results on feasibility and acceptability of the program are available in another report [27].

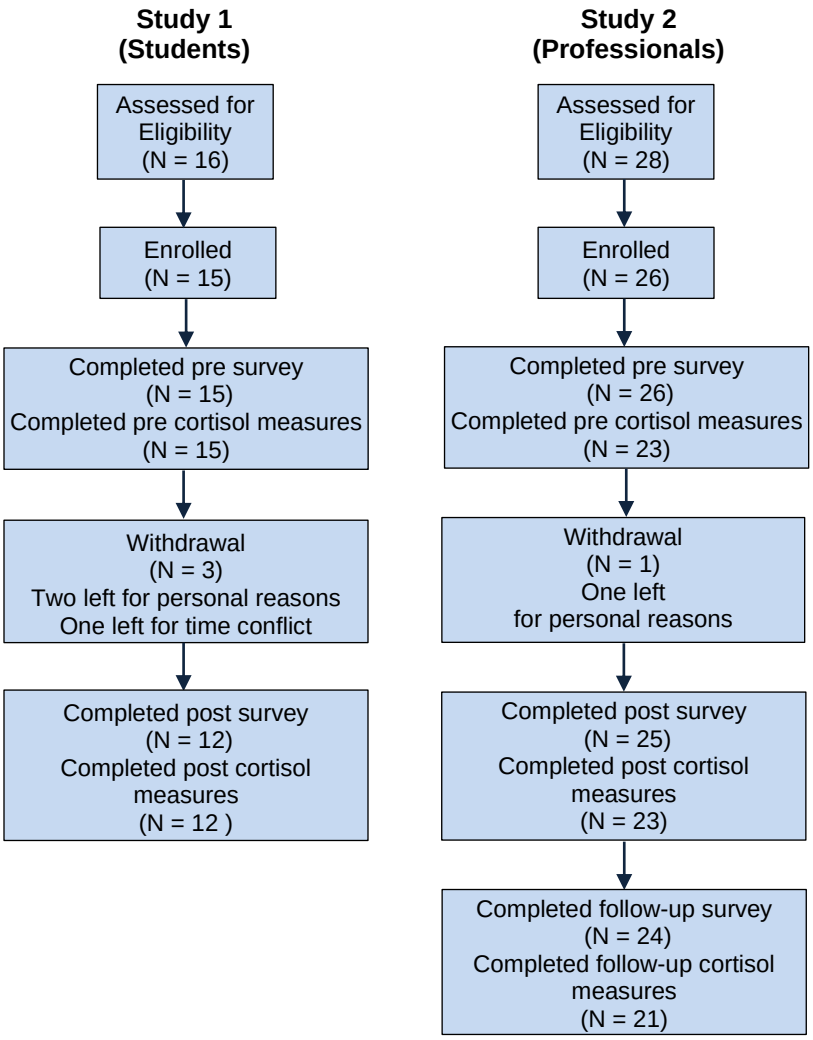

Figure 1. Flow diagram of the participants of Study 1 and Study 2. Analyses for self-reported mesures were carried out with data from 12 participants in Study 1 and 25 participants in Study 2. For cortisol measures, analyses were performed with data from 12 participants in Study 1 and 23 participants in Study 2. Note. N: number.

Table 1

Description of participants in the MBSR program from Study 1 (students) and Study 2 (hematology-oncology HCPs)

	Study I (Students, *n* = 12)	Study II (Professionals, *n* = 25)
	n (%) / *M* (*SD*)	*n* (%) / *M* (*SD*)
Sex		
Female	11 (92%)	22 (88%)
Male	1 (8%)	3 (12 %)
Age	24.0 (4.2) range 18-30	48.1 (10.8) range 27-63
Marital status		
Married, civil union, common-law	5 (42%)	12 (48%)
Single	7 (58%)	13 (52%)
University level (Study I) / Level of education (Study 2)		
College		3 (12%)
Bachelor	7 (58%)	12 (48%)
Master		6 (24%)
Doctorate	5 (42%)	4 (16%)
Profession (Study 2)		
Health Care Professionals		
Nurse	-	13 (52%)
Physician	-	2 (8%)
Professionals[a]	-	4 (16%)
Support Staff[b]	-	6 (24%)
Formal home practice (hrs/8 weeks)	9.8 (6.2)	24.9 (12.9)
Informal home practice (hrs/8 weeks)	2.5 (1.8)	11.4 (15.3)
Attended sessions (N)	7.0 (0.85)	6.9 (1.41)
Silent retreat participation	11 (92%)	19 (76%)
Hair characteristics (Baseline)		
Washes per week	3.26 (1.65)	4.06 (2.08)
Hair treatment	1 (8 %)	13 (52 %)

Note. MBSR: mindfulness-based stress reduction; HCPs: Healthcare practitioners; n: number; M: sample mean; SD: standard deviation; [a] 2 physiotherapists and 2 supportive care professionals; [b] 4 research staff and 2 community organization professionals.

3.1. Aim 1. Changes on biological and psychological stress

3.1.1. Study 1

The means and standard deviations of outcomes at different time points are available in Table S1. In the following lines, we emphasize the size of change observed in the studies. Full details with statistical testing are available in Fig. 2 and supplementary Tables. In Study 1, there was no statistically significant change in HCC pre-post intervention, mean diff. = –2.58, $p = 0.215$, $d = 0.38$, 95% CI [–1.74, 6.92]. We found statistically significant changes in psychological distress, anxiety, and exhaustion. Pre-post differences in perceived stress showed medium effect size, mean diff. = –2.83, $p = 0.081$, $d = 0.55$, 95% CI [–4.16, 6.08]. The same was observed for psychological distress, mean diff. = –6.08, $p < 0.05$, $d = 0.84$, 95% CI [–10.67, –1.50], anxiety, mean diff. = –2.16, $p < 0.05$, $d = 0.83$, 95% CI [–3.83, –0.50], and depression, mean diff. = –2.50, $p = 0.060$, $d = 0.61$, 95% CI [–5.12, –0.12]. Burnout domains also showed medium size differences: exhaustion, mean diff. = –2.41, $p < 0.05$, $d = 0.65$, 95% CI [–4.77, –0.06], depersonalization, mean diff. = –1.67, $p = 0.132$, $d = 0.47$, 95% CI [–3.92, –0.89], efficacy, mean diff. = 1.08 , $p = 0.250$, $d = 0.35$, 95% CI [0.88, 3.05] (Fig. 2). When considering cut-points, 42% of the students were considered cases on distress at baseline, a proportion dropping to 25% post-intervention, but this was not significant. Finally, among those with high levels of burnout at baseline ($n = 3/12$), no one showed such a level post-intervention ($n = 0/12$; no statistical testing available; Table S2 and S3).

3.1.2. Study 2

Similarly, we found no change in HCC, $F(2, 29.4) = 0.22$; $p = 0.806$) with negligible effect size in both pre/post and pre/follow-up comparisons ($d = 0.04$ and $d =$

0.00; Fig. 2 panel A; Table S4). In contrast, statistically significant improvements were observed in perceived stress, $F(2, 31.3) = 4.55$, $p < 0.05$), psychological distress, $F(3, 31.8) = 4.83$, $p < 0.05$), anxiety, $F(2, 28.5) = 5.24$, $p < 0.05$), and depression, $F(2, 31.8) = 4.34$, $p < 0.05$), but not in somatization, $F(2, 32.7) = 1.10$, $p = 0.353$).

On pre-post, perceived stress, mean diff. = –3.20, $p < 0.05$, $d = 0.51$, 95% CI [–5.43, –0.97], psychological distress, mean diff. = –4.76, $p < 0.01$, $d = 0.56$, 95% CI [–8.11, –1.41], anxiety, mean diff. = –1.64, $p < 0.05$, $d = 0.53$, 95% CI [–2.94, –0.34], and depression, mean diff. = –2.56, $p < 0.01$, $d = 0.58$, 95% CI [–4.35, –0.77], showed medium improvements (Fig. 2 panels C-E). As for burnout dimensions, very large improvements were observed, emotional exhaustion, mean diff. = –10.12, $p < 0.001$, $d = 1.12$, 95% CI [–13.66, –6.58], cynicism, mean diff. = –6.48, $p < 0.001$, $d = 1.95$, 95% CI [–7.76, –5.20], and personal accomplishment, mean diff. = 3.84, $p < 0.001$, $d = 0.97$, 95% CI [2.22, 5.46]. Importantly, these pre-post improvements were maintained over three months for most measures: psychological distress, mean diff. = –5.92, $p < 0.01$, $d = 0.93$, 95% CI [–9.86, –1.75], anxiety, mean diff. = –2.29, $p < 0.01$, $d = 0.86$, 95% CI [–3.92, –0.90], depression, mean diff. = –2.50, $p < 0.05$, $d = 0.66$, 95% CI [–4.72, –0.38], emotional exhaustion, mean diff. = –9.33, $p < 0.001$, $d = 1.06$, 95% CI [–14.04, –4.52], cynicism, mean diff. = –5.50, $p < 0.001$, $d = 1.88$, 95% CI [–7.15, –3.92], and personal accomplishment, mean diff = 2.58, $p < 0.05$, $d = 0.45$, 95% CI [0.03, 4.99]; Fig. 2 panels C–H. The full quantitative results are available in Tables S1 and S4.

These results were partly confirmed when exploring proportions of positives according to available cut-points on burnout but not on distress. Specifically, the proportion of those who scored high on burnout decreased significantly after the program,

by 48% (from 68% to 20%), 95% CI [25.5-70.5], $p < 0.01$. This change was maintained over three months at follow-up, with a decrease by 40% (from 68% to 28%), 95% CI [17.8-62.2], $p < 0.01$ (Table S2 and S3).

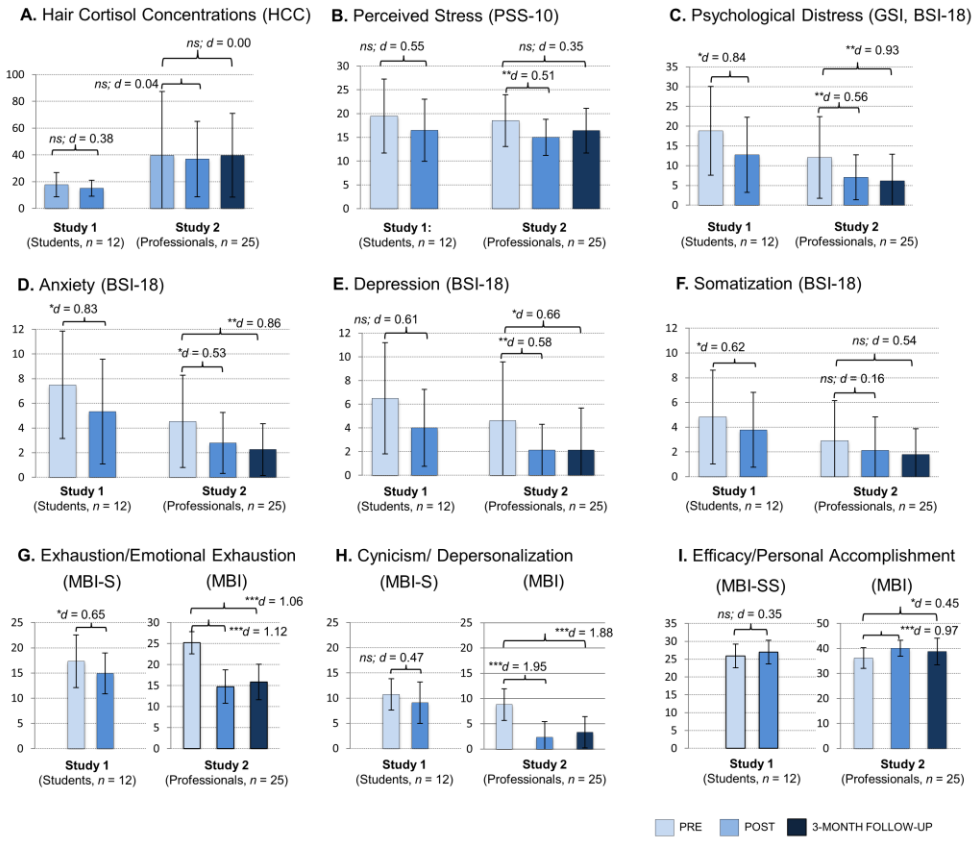

Figure 2. Changes in self-reported measures for Study 1 (12 university students) and Study 2 (25 hematology-oncology professionals) following the intervention. A. Change in perceived stress scores as measured by the Perceived Stress Scale (PSS-10). B. Change in hair cortisol concentrations in picogram per milligram (pg/mg) for the first scalp-near hair segment. C-F. Change in psychological distress scores, somatization scores, depression scores, and anxiety scores as measured by the Global Score Index (Brief Symptom Inventory; BSI-18). G-I. Change in emotional exhaustion scores, depersonalization scores, and personal accomplishment scores as measured by the Maslach Burnout Inventory (MBI). * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$; Cohen's *d:* 0.20 = small; 0.50 = medium; 0.80 = large. Note. ns: not significant; d: Cohen's d values.

We led supplementary analyses to examine concomitant change in biological and psychological measures. We found no evidence for systematic associations with median r = 0.433 (Study 1), and median r = 0.164 (Study 2). However, in Study 1, we found unexpected associations, where percent increases in HCC were associated with *decreases* in perceived stress (r = –0.667, p <.05), and with *increases* in efficacy (r = 0.583, p <.05). In Study 2, percent increases in HCC were associated with increases in somatization from the BSI-18 (r = 0.420, p <.05) (Fig. S1).

3.2. Aim 2. Factors associated with change over time

When exploring the role of intensity of practice, we observed no effect of home practice, formal (Study 1 median r = 0.23 and Study 2 median r = 0.18, not significant) or informal (Study 1 median r = 0.23 and Study 2 median r = 0.19, not significant). In contrast, we found that the attendance to the silent retreat (n = 19/25, 76%) was significantly associated with more favorable outcomes. In Study 1, attendance to the retreat related with larger change in efficacy (r = 0.62, p < 0.05). In Study 2, retreat attendance was significantly associated with larger changes in perceived stress (r = –0.52, p < 0.01) and personal accomplishment (r = 0.51, p < 0.01).

When correlating baseline stress with raw change on outcomes in Study 1, we found associations suggesting that higher initial stress would result into larger effects on psychological distress (r = –0.58, p < 0.05) and depression (r = –0.58, p < 0.05). In Study 2, higher baseline stress related with larger effects on perceived stress (r = –0.74, p < 0.01), psychological distress (r = –0.61, p < 0.01), depression (r = –0.71, p < 0.01), and depersonalization (r = –0.45, p < 0.05).

4. DISCUSSION

We led two studies to evaluate changes in a range of biological and psychological outcomes following an 8-week MBSR training. We found that the intervention was not associated with any notable change in hair cortisol concentrations in the target group of HCPs. In contrast, we observed medium-large effect sizes in a range of self-reported measures of psychological stress, emotional distress and burnout. These changes were consistent at three months, and were enhanced in participants attending the silent retreat, and those reporting higher baseline stress.

When comparing the present samples with samples from previous studies on biological stress, we found that Study 1 participants' hair cortisol levels at baseline were similar to levels reported from large samples of healthy individuals, with median $d = 0.15$ [37-39] (Fig. S2). However, in Study 2, participants' hair cortisol levels at baseline were significantly higher when compared to samples of healthy individuals, with median $d = 0.68$, and closer to a sample of non-professional caregivers ($d = 0.35$) [40]. For psychological stress, participants from both studies had significantly higher baseline levels of perceived stress when compared to published norms for individuals of the same age group (Study 1, $d = 1.07$; Study 2, $d = 1.32$) [41].

The stability on biological stress found here replicates the results from the only previous study investigating the impact of MBSR in HCPs' salivary cortisol levels [21]. Our findings could reflect an absence of biological change. One hypothesis is that it would require more practice over a longer time period to yield biological changes, as is suggested by a number of studies on experienced meditators [42,43]. The timing of the hair sample collection may also have influenced the results. Since the second collection (post) was done a month after the end of the program to respect the 3-month timeframe

necessary for hair sampling, it is possible that participants had stopped practicing after the program and thus the 3-month actually included time without practice. Research shows that salivary and plasma cortisol may be impacted by MBSR in patients' populations [16,44], but such results have not been consensual [20,45]. A recent study with professionals and students observed a significant decrease in hair cortisol, but not in salivary cortisol following a stress management program including meditation-guided imagery [25].

The absence of change in biological stress is in sharp contrast with the pre-post changes observed on self-reported measures. Globally, improvements in perceived stress have been a consistent result in this field [46-54]. Yet, this specific result was not maintained at 3 months after completion of the program (Study 2), which could be because some participants had stopped practicing after completing the program. This is in line with the only study evaluating the impact of an MBSR-based intervention in healthcare providers working in pediatric oncology [15], suggesting MBSR would not modify perceived stress as measured by the PSS, a measure also including a strong tone of lack of control.

Positive and consistent results on the different facets of emotional distress suggest that the intervention could have lasting effects in reducing distress symptoms in HCPs, as previous research has suggested [48,55]. This may occur as a result of increased emotional competencies resulting from enhanced mindfulness [27,56-59]. In fact, rather than fighting or avoiding painful emotions, mindfulness training leads participants to observe them without judgment, a process similar to principles of exposure used in anxiety treatment [60]. Medium to large effect sizes were observed on anxiety (in average a pre-post 39 %

decrease in the HCP group), suggesting MBSR would target ruminative cycles and anticipatory thinking that are a core part of anxiety.

Turning to burnout, the durable improvements observed in emotional exhaustion and depersonalization are consistent with results previously reported in studies using the same measure with HCPs [21,54,61-66]. These results are encouraging, given the high frequency of this issue among HCPs in pediatric hematology-oncology [1,67]. Mechanisms underlying the reduction in burnout should be investigated in future studies (48% decrease in the proportion of participants with high levels of burnout in our target group). One explanation could pertain to "the ability to be in the present moment", a core competence that MBSR is deemed to train. This would allow meditators to *respond* to stress instead of *reacting* to it, i.e. change their relationships with the stressors, help them see new options and choose more adaptive behaviors [68].

The impact on psychological stress is an essential aspect of MBSR, as it suggests it changes one's own experience with stress. As our results suggest, self-reported measures are crucial in this type of research because stress remains largely a subjective experience, being influenced by how we perceive situations [69]. Yet, this effect on one's experience cannot be disentangled from desirability, or positive attitude toward the intervention. As a counterbalance to this interpretation, we found changes in some psychological measures to be associated with changes in cortisol concentrations, suggesting that changes in the experience of participants could be related to changes in biological stress. In the target group of HCPs, very few significant associations were found between stress measures. We only found that increases in HCC were associated with increases in somatization. This contrasts with recent research indicating that

somatization was associated with a reduced cortisol response [70]. Our result suggests that the differential patterns of HPA-axis dysregulation in relation to psychological outcomes is still unclear. For instance, in the smaller group of students from Study 1, the results point to a reduction of perceived stress and burnout to be associated with *increased* HCC. It is possible that some of these limited findings may be the result of more complex interaction and nonlinear associations [23,71]. Of course, our paradoxical results could also be partially explained by the small sizes of our samples. More research with larger groups is definitively needed on this topic, as associations between stress measures are not univocal (see detailed discussion in [72]).

The positive role of attendance to the silent retreat on improvements in perceived stress and personal accomplishment is notable. Performing additional analyses, we calculated the coefficient of determination (R^2) and found that the attendance to the silent retreat accounted for 19.3% of the variance in the reduction of perceived stress, and 23% of the variance in the increase of the burnout dimension of personal accomplishment. These preliminary results suggest that this specific component of MBSR may play an important role. Meditation retreats have already been linked to improvements in anxiety, depression, and stress [73]. A detailed component analysis is needed, as the results suggest that not all components are equally efficient on outomes.

As expected, those who showed higher levels in psychological stress at baseline were more prone to improve on a range of measures, including stress, psychological distress, and depression. This points to some limit in the ability of MBSR to improve perceived stress when stress is not elevated. It is probable that the benefits of MBSR, as a

stress-reduction technique, would be enhanced in people in need of reducing their stress, such as HCPs here, as their stress levels were higher than in the other group.

We should recognize the limitations of this research. Firstly, as we did not have a control group, it was not possible to attribute changes over time to the intervention itself. Yet, we were able to reach our goal of identifying the size of changes allowing us to generate further hypotheses and possibly inform calculations of sample sizes for future efficacy research [26]. Interestingly, among the range of outcomes evaluated in the target group of HCPs, further research should probably focus on anxiety, burnout, emotional distress, and perceived stress. Secondly, although we focused on effect sizes at this stage of research, the sample sizes were small, limiting the transferability of results to other samples. Thirdly, professionals were self-selected and were predominantly women. Therefore they were not representative of the population of HCPs. We also should recognize that two subscales of burnout (cynicism and personal accomplishment) had low consistencies and should thus be interpreted with caution. Finally, we did not control for medications that might have interfered with the secretion of cortisol. Thus we cannot rule out that the stability on HCC might be biased.

5. CONCLUSION

In summary, in a one-group intervention design performed in two samples (students and HCPs) being trained in mindfulness with an MBSR-based program, we found no change in biological stress. Yet, we found medium-large pre-post changes in a range of outcomes including anxiety, exhaustion (burnout), perceived stress, and depression, with some changes remaining consistent over time. We also found that one component of the intervention, the silent retreat, moderated improvements on self-

reported stress measures. The results suggest that the most promising outcomes to select in hematology-oncology HCPs would be emotional exhaustion, cynicism, and psychological distress. In this population, interventionists could expect medium-large effect sizes on such self-reported outcomes. Despite the absence of positive results with HCC in the present research, future studies should explore the biological markers of chronic stress in relation to mindfulness in standard programs such as MBSR, as these may contribute to better understand the effects of stress reduction independently of positive attitudes toward mindfulness, the training, or the interventionist.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Table S1

Study 1 and Study 2 outcomes scores at different time-points

	Study 1 (Students)					*Study II (Professionals)*							
	Pre (*n* = 12) (HCC *n* = 12)		*Post* (*n* = 12) (HCC *n* = 12)			*Pre* (*n* = 25) (HCC *n* = 23)		*Post* (*n* = 25) (HCC *n* = 23)			*Follow-up* (*n* = 24) (HCC *n* = 21)		
Measure	*M*	*SD*	*M*	*SD*	*p*	*M*	*SD*	*M*	*SD*	*p*	*M*	*SD*	*p*
HCC (pg/mg)	17.76	9.14	15.18	5.95	0.215	37.34	46.11	35.84	27.18	0.834	39.67	31.28	0.864
PSS-10	19.50	7.79	16.67	6.55	0.081	18.60	5.35	15.40	4.23	0.006	16.42	4.69	0.139
BSI-18													
GSI	18.83	11.22	12.75	9.55	0.014	12.36	10.23	7.60	6.22	0.007	6.17	6.77	0.006
Anxiety	7.50	4.36	5.33	4.25	0.015	4.84	3.94	3.20	3.18	0.015	2.25	2.09	0.003
Depression	6.50	4.70	4.00	3.25	0.060	4.64	4.84	2.08	2.14	0.007	2.13	3.54	0.022
Somatization	4.83	3.79	3.42	3.01	0.054	2.88	3.15	2.32	2.82	0.404	1.79	2.09	0.153
MBI-SS / MBI													
Exhaustion/Emotional Exhaustion	17.33	5.21	14.92	4.03	0.045	25.40	7.15	15.28	8.37	0.000	15.88	10.27	0.000
Depersonalization/Cynicism	10.75	3.12	9.08	4.12	0.232	8.84	3.53	2.33	2.82	0.000	3.29	3.13	0.000
Efficacy/Personal Accomplishment/	25.92	3.32	27.00	3.30	0.250	36.40	4.18	40.24	3.22	0.000	38.79	5.23	0.048

HCC = Hair cortisol concentration; PSS = Perceived Stress Scale; GSI = General Severity Index; BSI = Brief Symptom Inventory; MBI-SS= Maslach Burnout Inventory-Student Survey; MBI = Maslach Burnout Inventory

p values are for changes over time in Study 1 (Student's paired t tests) and Study 2 (estimates of fixed effects of time)

Table S2

Evolution in BSI-18 caseness and MBI burnout status before the MBSR program, after (week 8) and at follow-up (week 20) in Study 1 and Study 2

DISTRESS (BSI-18)	Caseness Pre	Caseness Post	Caseness Follow-up	% Decrease and 95% CI	*p* Value
Study 1 Students (*n* = 12)	41.7 %	25.0%		16.7% (-4.0, 38.0)	0.500
Study 2 Professionals (*n* = 25)	16.0 %	4.0 %		12 % (-4.9, 28.9)	0.370
Study 2 Professionals (*n* = 25)	16.0 %		4.0 %	12 % (-4.9, 28.9)	0.370
BURNOUT (MBI)	High Burnout Pre	High Burnout Post	High Burnout Follow-up		
Study 1 Students (*n* = 12)	25.0%	0.0%		25%	NA[a]
Study 2 Professionals (*n* = 25)	68.0%	20.0%		48% (25.5, 70.5)	0.002
Study 2 Professionals (*n* = 25)	68.0%		28.0%	40% (17.8, 62.2)	0.006

[a]Computed only for a PxP table, where P must be greater than 1.

High level of student burnout = high score on the EX subscale (≥ 23), a high score on the CY subscale (≥ 18) or a low score on the on the EF subscale (≤ 16). High level of professional burnout = high score on the EE subscale (≥ 27), a high score on the DP subscale (≥ 10) or a low score on the on the PA subscale (≤ 33).

Table S3

Frequency of burnout status according to time points in Study 1 and Study 2

	Study 1		Study 2		
	Pre (*n* = 12) (%)	Post (*n* = 12) (%)	Pre (*n* = 25) (%)	Post (*n* = 25) (%)	Follow-up (*n* = 24) (%)
Overall burnout[a]	25	0	68	20	28
Exhaustion /Emotional Exhaustion					
High	25	0	40	12	16
Moderate	58	58	44	20	28
Low	17	42	16	68	52
Cynicism/Depersonalization					
High	0	0	44	4	0
Moderate	58	33	36	12	24
Low	42	67	20	84	72
Efficacy/Personal Accomplishment					
High	0	0	28	4	12
Moderate	67	0	52	32	40
Low	33	100	20	64	44

Burnout levels were assessed according to reported cut-off for Study 1 and the MBI manual cut-offs for Study 2.

[a] Overall burnout was defined as a high score on the Exhaustion/Emotional Exhaustion subscale, a high score on the Cynicism/Depersonalization subscale or a low score on the Efficacy/Personal Accomplishment Subscale.

Table S4

Study 2 estimates of fixed effects of time in pediatric hematology-oncology professionals on outcomes before the MBSR program, after the program, and at follow-up (n = 25)

	Estimate	*SE*	*df*	*t*	*p*	*d*	Estimate 95% CI
			HCC (pg/mg)				
Time (t_1–t_2)	–1.497	7.072	23.36	0.212	0.834	0.04	[–16.11, 13.12]
Time (t_1–t_3)	1.508	8.763	36.04	–0.172	0.864	0.00	[–16.26, 19.28]
			PSS-10				
Time (t_1–t_2)	–3.200	1.096	33.30	2.92	0.006	0.51	[–5.43, –0.97]
Time (t_1–t_3)	–2.006	1.33	45.20	1.51	0.139	0.35	[–4.69, 0.68]
			Psychological Distress (GSI; BSI-18)				
Time (t_1–t_2)	–4.760	1.631	26.01	2.919	0.007	0.56	[–8.11, –1.41]
Time (t_1–t_3)	–5.805	2.004	39.14	2.896	0.006	0.93	[–9.86, –1.75]
			Anxiety (BSI-18)				
Time (t_1–t_2)	–1.640	0.639	30.30	2.57	0.015	0.53	[–2.94, –0.34]
Time (t_1–t_3)	–2.410	0.747	37.38	3.23	0.003	0.86	[–3.92, –0.90]
			Depression (BSI-18)				
Time (t_1–t_2)	–2.560	0.869	24.78	2.95	0.007	0.58	[–4.35, –0.77]
Time (t_1–t_3)	–2.550	1.074	42.25	2.38	0.022	0.66	[–4.72, –0.38]
			Somatization (BSI-18)				
Time (t_1–t_2)	–0.560	0.663	34.68	0.84	0.404	0.16	[–1.91, 0.79]
Time (t_1–t_3)	–1.031	0.708	40.92	1.46	0.153	0.54	[–2.46, 0.40]

Emotional Exhaustion (MBI)							
Time (t_1–t_2)	–10.120	1.747	36.31	5.79	0.000	1.12	[–13.66, –6.58]
Time (t_1–t_3)	–9.279	2.356	40.97	3.94	0.000	1.06	[–14.04, –4.52]
Cynicism (MBI)							
Time (t_1–t_2)	–6.480	0.629	32.58	10.31	0.000	1.95	[–7.76, –5.20]
Time (t_1–t_3)	–5.532	0.802	45.98	6.89	0.000	1.88	[–7.15, –3.92]
Personal Accomplishment (MBI)							
Time (t_1–t_2)	3.840	0.795	32.04	–4.83	0.000	0.97	[2.22, .5.46]
Time (t_1–t_3)	2.507	1.229	43.35	–2.04	0.048	0.45	[0.03, 4.99]

HCC = hair cortisol concentration; PSS = Perceived Stress Scale; GSI = Global Severity Index; BSI = Brief Symptom Inventory; MBI = Maslach Burnout Inventory; t_1 = *pre;* t_2 = *post;* t_3 = follow-up.

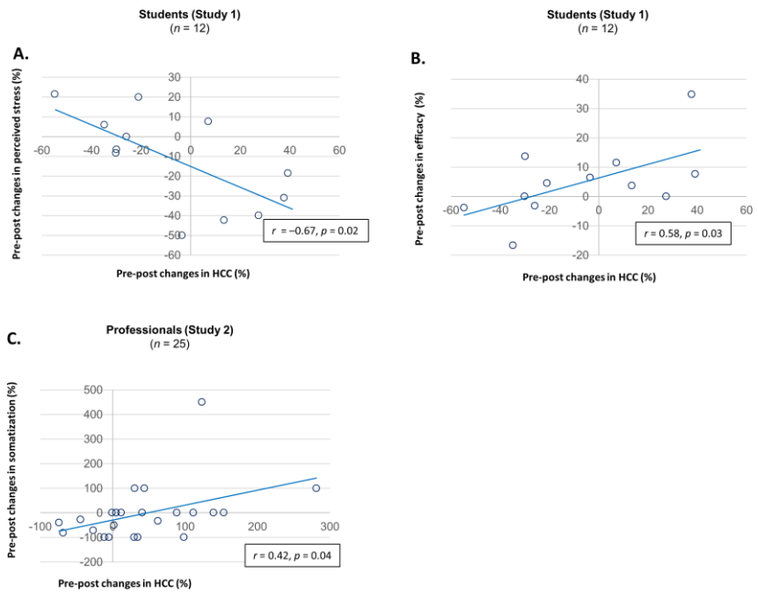

Figure S1. Associations between proportional changes in biological stress (cortisol) and psychological stress (PSS-10). **A.** Association between percentage of pre-post changes in HCC and percentage of pre-post changes in perceived stress (PSS-10) scores in Study 1. **B.** Association between percentage of pre-post changes in HCC and percentage of change in Efficacy (burnout dimension) in Study 1. **C.** Association between percentage of pre-post changes in HCC and percentage of change in somatization (BSI-18) in Study 2.

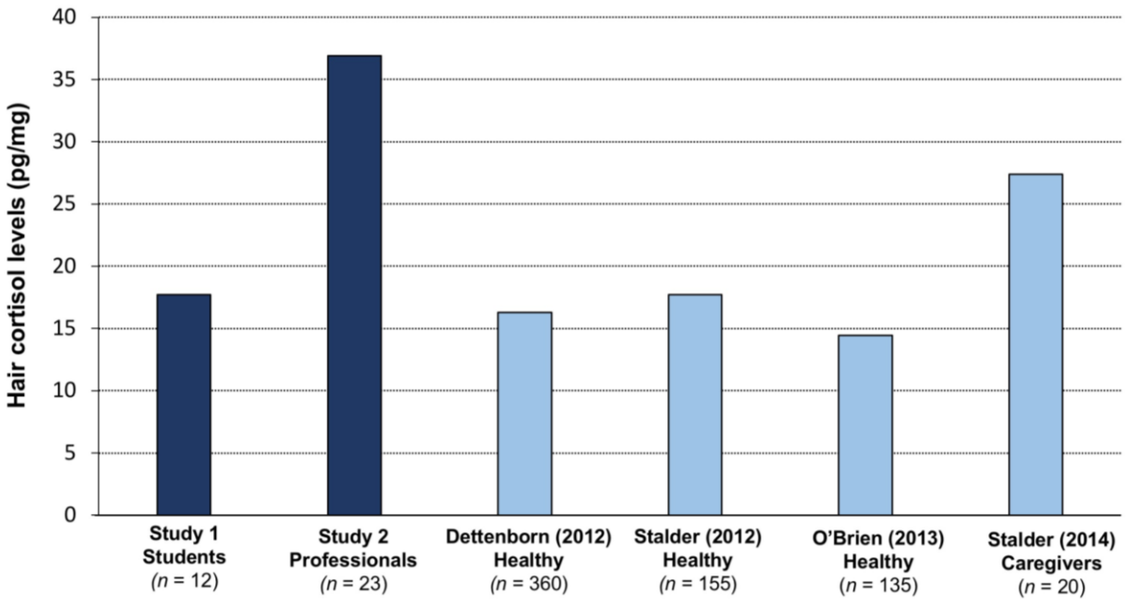

Figure S2. Hair cortisol levels at baseline compared with samples from previous studies. Comparisons of hair cortisol levels at baseline with levels reported in the literature for large samples of healthy individuals and professional caregivers.