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Effectiveness of a Mindfulness-based Intervention on Groups with Presence/ Absence of Clinically Significant Depressive Symptoms

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ABSTRACT

Depressive symptoms have an important effect on everyday life. Its development could be associated with a lack of metacognitive skills among other variables. It seems they can be trained by an intervention based in meditation techniques called mindfulness based intervention. The aims of this study were to evaluate 1) the relationship between depressive symptoms, emotional regulation, and metacognitive skills, 2) the effectiveness of an eight-week mindfulness based intervention program on depressive symptoms, metacognition, and emotional regulation in non-clinical population, and 3) the different effect of this intervention on people with presence/absence of clinically significant depressive symptoms. Sixty-seven participants received mindfulness training on a weekly basis during two months. Data on metacognition, emotional regulation, and depressive symptoms was collected one month before the intervention, the first and last day of the intervention, and at 3-month follow up. Significant correlations were found for the total sample and the presence/absence of clinically significant depressive symptoms groups. Differences were found with larger effect sizes in the depressive group ($\eta^2 = .73-.99$) than in the group with no depressive simptoms ($\eta^2 = .41-.70$). These results support mindfulness intervention as an effective technique in the alleviation of depressive symptoms and in the improvement of metacognitive skills.

Eficacia de una intervención basada en *mindfulness* en grupos con presencia/ ausencia de síntomas depresivos clínicamente significativos

RESUMEN

Los síntomas depresivos tienen un efecto importante en la vida cotidiana. Su desarrollo podría asociarse entre otras variables con una falta de habilidades metacognitivas. Parece que estas pueden ser entrenados por una intervención mediante técnicas de meditación basada en *mindfulness*. Los objetivos de este estudio fueron evaluar: 1) la relación entre los síntomas depresivos, la regulación emocional y las habilidades metacognitivas, 2) la eficacia de un programa de intervención basado en *mindfulness* de ocho semanas en los síntomas depresivos, metacognición y regulación emocional en población no clínica y 3) el efecto diferente de esta intervención en personas con presencia/ausencia de síntomas depresivos clínicamente significativos. Sesenta y siete participantes recibieron un entrenamiento semanal en *mindfulness* durante dos meses. Los datos sobre la metacognición, la regulación emocional y los síntomas depresivos se recogieron un mes antes de la intervención, el primer y último día de la intervención y a los 3 meses de seguimiento. Se encontraron correlaciones significativas para la muestra total y la presencia/ausencia de grupos de síntomas depresivos clínicamente significativos. Las diferencias se encontraron con tamaños de efecto más grandes en el grupo depresivo ($\eta^2 = .73-.99$) que en el grupo sin síntomas depresivos y la mejora de las habilidades metacognitivas.

Depression is an emotional reaction towards stressful situations whose excessive intensity or duration can interfere in people's life (American Psychiatric Association, 2013). A survey conducted by the ESEMed with Spanish population points out major depressive disorder as the mental condition with the highest prevalence throughout life (10.5%) followed by specific phobia (4.5%) and dysthymia (3.7%) (Haro

et al., 2006). These prevalence rates reflect a small proportion of the depressive spectrum. This condition has different forms and one of them which does not commonly appear in these rates is the subclinical depression or depressive symptomatology (Rivas, Nuevo, & Ayuso-Mateos, 2011). Despite not reaching the standard criteria for depression, these symptoms have an important effect on people's well-being.

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There are different factors that may affect the development of depressive symptoms. Psychological factors are among the most influential factors. In this line, there are several models which have studied the characteristics of the development and maintenance of depressive symptoms in depth. The cognitive model is one of them (Beck, 1983). This model points out the importance of the interpretation of the event in the development of depressive symptomatology rather than the event per se. When experiencing a negative life event, some people may have thoughts of blaming themselves or others, sense of catastrophe, or dwell on ruminating, whereas other people may have thoughts of positive reappraisal of the situation (Garnefski, Krajj, & Spinhoven, 2001). The cognitive model highlights the role of negative cognitions and maladaptive coping strategies (catastrophic thinking or self-blaming) in the development of depressive symptoms (Aldao, Nolen-Hoeksema, & Schweizer, 2010).

Nevertheless, some studies have pointed out that people with the same negative cognitions showed great differences in the expression of their symptoms (Flavell, 1979). Likewise, one of the models working under the cognitive paradigm argued that one possible root of these differences could lie in the processes which monitor these cognitions (Teasdale et al., 2000). These processes are named metacognitions and the model that studies them is called metacognitive model. Metacognitive processes involve the capacity to reflect about oneself and one's mental functioning. It refers to the capacity to observe one's tendency to relate with own mental content. One can be aware of the way one experiences sadness and reacts to this feeling. For example, one person with metacognitive skills would be aware of the overwhelming tendency to interact with sadness (rumination) and become able to understand this content as something impermanent and subjective, opened to different forms of experiencing it. On the other hand, a person with metacognitive deficits would be trapped in, overwhelmed with, or dissociated from sadness without being aware enough to change this pattern (Teasdale et al., 2002; Wells & Matthews, 1996).

As it can be seen, metacognitive deficits could lead people to develop constant emotional regulation patterns such as rumination or dissociation, commonly related to the development of depressive symptoms. On the other hand, metacognitive skills seem to be related to the development of the capacity to put mental contents in another perspective or accept one's needs (Aldao et al., 2010; Garnefski et al., 2001). These abilities allow people to meet their necessities more accurately or connect with alternative meanings gaining new strengths (Getch et al., 2014). This flexibility to face adversities transforms them in a possible source of personal growth, also known as resilience. Resilience refers to the capacity of adaption which people show in the face of significant adversity, tolerating it and connecting with personal sources or with others, seeking help for a positive adaptation (Luthar, Cicchetti, & Becker, 2000). Contrary to the above mentioned dysfunctional maladaptive emotional regulation patterns, these patterns increase a sense of well-being and connectedness (Shapiro, Brown, Thoresen, & Plante, 2011). Thus, beyond the type of thoughts that occupy the mind of depressed people, the metacognitive model examines how depressed people relate to their thoughts arguing for metacognitive deficits (Teasdale et al., 2000).

One of the most frequently used techniques in the field of metacognitive therapy is mindfulness based interventions (Jankowski & Holas, 2014; Teasdale, 1999), showing evidence of reducing the risk of relapse in recurrent depression and suffering in current depressive states (Van der Velden et al., 2015), and increasing both well-being (Gu, Strauss, Bond, & Cavanagh, 2015) and resilience (Pidgeon & Keye, 2014). These interventions have also proved their effectiveness in non-clinical populations reducing levels of stress and increasing levels of well-being, taking perspective or empathy (Zenner, Herrnleben-Kurz, & Walach, 2014). It seems that

mechanisms which operate under mindfulness interventions are attentional control, mindful awareness, and decentering among others. The concept of decentering is very similar to metacognition. It implies the recognition of subjective reality every one builds and the impermanence of emotions. People gain distance from their mental contents and do not identify themselves with them (Getch et al., 2014). Being mindful implies having an attitude able to pay attention towards mental contents from the present non-judgmentally (Kabat-Zinn, 1994). Interventions under this model involve training in attentional and other metacognitive skills through meditation techniques. These meditation techniques can be practiced formally by sitting meditation, yoga movements, and body scan, or informally by paying close attention to daily activities such as eating or emotionally challenging situations (Zenner et al., 2014).

As a consequence, this study has three aims: 1) to evaluate the effectiveness of a mindfulness based intervention program on depressive symptoms, metacognition, and emotional regulation in non-clinical population, 2) to evaluate the different effect of this intervention in people with presence vs absence of clinically significant depressive symptoms, and 3) to evaluate the relationship between depressive symptoms and emotional regulation and metacognitive skills after the intervention.

Method

Participants

Sixty-seven individuals participated in the study. Ages ranged from 20 to 67 years old, with a mean of 43.80 (SD = 12.10).

Table 1. Descriptive Statistics of the Total Sample and the Two Sub-samples

	Total	sample	No depre		Depressive		
	N %		N	%	N	%	
Gender							
Male	11	16.9	37	80.4	2	13.3	
Female	54	83.1	9	19.6	13	86.7	
Studies							
Tertiary education	58	84.4	45	82.2	14	93.3	
Secondary education	2	3.1	2	4.4			
Technical studies	6	9.4					
Primary studies	1	1.6			1	6.7	
Marital status							
Married or engaged	33	50.8	25	54.3	5	33.4	
Single	25	38.5	16	34.8	8	53.3	
Divorced	6	9.2	3	10.9	1	6.7	
Widowed	1	1.5			1	6.7	
Total	67		46		15		

Participants were academicians and administrators working at a middle size private university in Northern Spain (University of Deusto) where a mindfulness intervention program was offered to the campus community. The criterion for inclusion was being older than 18 years. All the participants were informed about the commitment to the intervention and the resolution of possible questions by them in an interview. The sample was divided in two groups according to the presence/absence of clinically significant depressive symptoms following the criteria of the depressive symptoms instrument (Center for Epidemiologic Studies Depression Scale; Vázquez, Blanco, & López, 2007). The cut off criteria was a result above 26 points in the total scale of the instrument of depressive symptoms. Originally, the cutoff used to discriminate the presence of depression was ≥ 16 (Fechner-Bates, Coyne, & Schwenk, 1994). However, this approach was widely criticized for not meeting the criteria of specificity and

sensitivity. Following such a criticism, more recent research suggests other points tighter cut between 24 and 27 (Vázquez et al., 2007), which was the one used in this research.

The group with absence of depressive symptoms was formed by 46 people with a mean of 44.16 years (SD = 12.26). The group with presence of clinically significant depressive symptoms was formed by 15 people with a mean of 42.5 years (SD = 12.39).

Descriptive statistics of the total sample and the two subsamples are detailed in Table 1.

Instruments

Depression. Center for Epidemiologic Studies Depression Scale (CESD; Radloff, 1977). It is a screening tool for depressive symptoms. It is one of the most commonly used instruments for measuring depressive symptoms worldwide. The Spanish adaptation by Vázquez et al. (2007) was used. It is a self-administered scale consisting of 20 items. Each item is answered according to a Likert-type scale response format with four options, ranging from 0 (*rarely or never*) to 3 (*most of the time*). It provides a score of depressive symptoms for the previous week. Scores can also be obtained for four subscales: depressed affect, positive affect, somatic and retarded activity, and interpersonal subscales. The internal consistency of the instrument in the present study was high (from .71 to .91) similar to the original Spanish instrument in which the total scale reached an alpha of .89 (Vázquez et al., 2007).

Mindfulness. Five Factors Questionnaire Mindfulness (FFMQ; Baer, Smith, Hopkins, Krietemeyer, & Toney, 2006). The instrument assesses mindfulness through five independent factors; 1) observing – sensory, emotional and cognitive aspects of internal and external experience –, 2) describing – the ability to symbolize the experience into words –, 3) acting with awareness – acting with consciousness –, 4) no judging – permissiveness and acceptance of inner experience –, and 5) no reactivity – no acting or feeling experiences with distance (Cebolla et al., 2012). These aspects are evaluated with 39 items that are answered with a 5-point Likert scale, ranging from *never or very rarely* to *often or always*. The Spanish adaptation showed a good internal consistency with a Cronbach's alpha between.75 and.91. In this study Cronbach's alphas were between .71 and .91.

Decentering Experiences Questionnaire (EQ; Fresco et al., 2007). It measures the ability to observe thoughts and emotions as mental events and not as defining aspects of the self (metacognition). The original scale was formed by 18 items with two subscales, rumination and wide perspective (Fresco et al., 2007). The validated instrument in the Spanish population was reduced to one scale formed by 11 items with a 5-point Likert scale ranging from *never* to *all the time* (Soler et al., 2014). In the original instrument, the alpha found was .83 (Fresco et al., 2007). The instrument also showed good internal properties in this study reaching .78

Resilience. The instrument used for measuring resilience was the Resilience Scale by Wagnild and Young (1993). This scale has been validated in Spanish in two different studies showing good psychometrical properties (α = .93) (Ruiz, de la Vega, Poveda, Rosado, & Serpa, 2012). The scale measured "personal competence" and "acceptance of self and life". The first factor represented personal strengths and self-efficacy such as independence, determination, invincibility, mastery, and perseverance. The second factor refers to adaptability, flexibility, and a balanced outlook of life. The instrument is formed by 25 items with a 7-point Likert scale ranging from *totally disagree* to *totally agree*. The alpha of the instrument in this study reached a coefficient of .89 as in the Spanish validation (Ruiz et al., 2012).

Cognitive coping strategies. Cognitive coping strategies were measured with the Cognitive Emotion Regulation Questionnaire

(CERQ; Garnefski et al., 2001). The CERQ consisted of 18 items and nine conceptually different subscales: adaptive strategies (acceptance, positive refocusing, refocus on planning, positive reappraisal, and putting into perspective) and less adaptive strategies (self-blame, rumination, catastrophizing, and otherblame) were identified (Domínguez-Sánchez, Lasa-Aristu, Amor, & Holgado-Tello, 2011). Each of the items is measured in a Likert scale, ranging from *never* to *always*. In the Spanish validation study alphas ranged from .60 to .86 (Domínguez-Sánchez et al., 2011). The alphas obtained in this study ranged from .59 to .84.

Procedure

Participants were contacted through the dissemination of a leaflet in which the intervention was explained. Mindfulness intervention was based in the Mindfulness Based Stress Reduction Program (Kabat-Zinn, 1994). Several changes in the original program were introduced. It consisted of 8 weekly sessions of 1 hour and 45 minutes instead of the 2 hours and 30 minutes of the original program and yoga techniques were replaced by visualizations. No further changes regarding the original program structure were made. People interested in the intervention were summoned to a preliminary interview in which they were informed of their commitment to attend the mindfulness intervention as well as the evaluation of participation. Intervention was carried out by professionals trained in the mindfulness-based stress reduction program by Kabat Zinn (1994).

Participants were assessed at four points in time: one month before the intervention (waiting list), pre-test (just before beginning the intervention), post-test (just after finishing the last session of the intervention), and follow-up (three months after the intervention). Evaluations were conducted online or in paper depending on participants' choice. No differences were reported (Fernandez, 2015).

The intervention took place during the years 2012, 2013, and 2014. The intervention was conducted in 8 different groups during these years following the same program and times of assessment. Each group was formed by a maximum of 10 people with no previous knowledge of mindfulness technique. Participants contacted for the intervention belonged to the same population area. The research group respected the law of data protection using a numeric code that ensure participants' anonymity. This research had the ethical approval from the University of Deusto and BIOEF (Basque Foundation for Innovation and Research) agency.

Data Analysis

The data analysis comprised a series of five repeated measures MANOVA to analyze changes in the scores through the four stages (waiting list, first day of intervention, last day of the intervention, and follow-up). In all the cases, both significance and effect size (η^2) were computed. This last one was interpreted following Cohen's criterion: values between .01 and .04 were considered small; between .05 and .14 medium, and above .14 large (Cohen, 1988).

Besides, in each analysis a multivariate effect (Pillai's trace) was analyzed first. Sphericity was also checked with Mauchly's W test. When sphericity was not assumed, the Greenhouse-Geisser degrees of freedom correction test was applied. In order to ease readiness of results, in absence of information sphericity was assumed.

When the multivariate test reached significance, univariate comparisons were computed and checked. In some of the univariate comparisons signification was attained, and then specific differences through the four stages were analyzed in each variable with Bonferroni post hoc test.

Table 2. Univariate Comparisons in Depressive Symptomatology, Coping, and Metacognitive Skills

	Waiting	Waiting list		Pre-test		Post-test		3-month follow-up		2
	M	SD	M	SD	M	SD	M	SD	- г	η²
Observe	24.57 ³	7.18	25.07 ^{3,4}	4.56	29.351,2	4.84	28.57 ²	3.87	7.08*	.35
Describe	30.64	4.78	28.21	2.57	31.42	4.12	31.14	4.07	3.01	.18
Act with awareness	24.28	5.16	27.78	3.74	24.28	4.56	24.92	4.37	2.18	.14
No judgement	26.42	6.51	23.35	5.71	30.00	4.83	29.35	5.34	3.62	.21
No reactivity	20.57	2.84	23.35	3.45	21.28	2.61	22.92	2.52	3.13	.19

Note. ¹Differences between the score in this phase and the score in the waiting list according to the Bonferroni's post hoc test; ¹waiting list; ²pre-test; ³post-test; ⁴3-month follow-up.

Results

First, differences in mindfulness were explored. A multivariate significant effect was obtained, F(15, 111) = 2.39, p = .005, $\eta^2 = .24$. Then, specific differences in the four variables comprising mindfulness were tested. In the first three variables, sphericity was not assumed. The univariate contrasts as well as post hoc test are detailed in Table 2. As it can be observed, significant differences were attained only in observation, so in general in the post-test and in follow-up stages scores increased regarding the waiting list and the pre-test stages.

Second, differences in empathy were analyzed. As this is a single variable, no multivariate test was conducted. Univariate comparison showed a significant effect, F(15, 45) = 13.54, P < .001, $P^2 = .47$. The Bonferroni post hoc test showed that the scores in the pre-test (P = 34.56, P = 4.05) were significantly lower than in the post-test (P = 42.06, P = 3.82) and in the follow-up stage (P = 40.69, P = 2.55).

Third, differences in depression were analyzed. A significant multivariate effect was attained, F(12, 4) = 6.45, p < .001, $\eta^2 = .95$. Univariate comparisons are showed in Table 3. As it can be observed, there was only a significant effect in positive affect, which was increased in the post-test and follow-up stages in comparison to the waiting list.

Fourth, differences in coping were analyzed. A significant multivariate effect was obtained, F(27, 108) = 3.19, p < .001, $\eta^2 = .44$. Univariate comparisons are showed in Table 4. As it can be observed, all the variables attained significance except rumination, planification, and other-blame. In general, scores in the follow-up stage were higher than in the pre-test stage.

Fifth, differences in resilience were analyzed. Multivariate differences were not evidenced, F(6, 9) = 0.61, p = .717, $\eta^2 = .29$, so univariate analyses were not conducted.

Discussion

The first aim of this study was to analyze the relationship between depressive symptoms and cognitive and metacognitive and emotional regulation variables. Data from the total group and groups with presence/absence of clinically significant depressive symptoms showed same directions in the correlations. This means the three groups showed that depressive symptoms correlated negatively with metacognitive skills and adaptive coping strategies and positively with maladaptive coping strategies. These relationships are supported by previous research in which depressive symptoms are associated with metacognitive deficits (Pearson, Brown, Bravo, & Witkiewitz, 2014) and maladaptive strategies (Aldao et al., 2010). Data from total group showed greater significance. These results could be affected by the sample size.

Data from statistical analyses have shown that mindfulness training reduces depressive symptoms and its effects would last for three months. These results are consistent with previous studies showing the effects of mindfulness intervention in depressive symptoms (Radford et al., 2014; Strauss, Cavanagh, Oliver, & Pettman, 2014; Van Aalderen et al., 2012). Changes which specifically lasted that long were those related to the positive affect in depressive symptoms. These results support previous literature which points out that mindfulness interventions alleviate depressive symptoms and underlies increases in the sense of well-being. The broaden attention gained from the mindfulness intervention enables depressed people to be aware about positive content previously ignored because of the effect of depressive symptoms (Gu et al., 2015).

Additionally, changes of depressive symptoms in the group of absence of clinical depressive symptoms confirm, coherently with previous studies, that mindfulness training can be beneficial also for people who do not show high rates of depressive symptoms (Khoury, Sharma, Rush, & Fournier, 2015).

Secondly, effects of mindfulness based intervention in metacognitive and emotional regulation were analyzed. Results show that after the intervention there are changes in adaptive coping style (positive focusing) and in maladaptive coping style (catastrophizing) in the total group. Meanwhile, results show a significant reduction of maladaptive strategies (catastrophizing) in the group with depressive symptoms and an increase in adaptive strategies (positive focusing, positive reappraisal, putting into perspective and personal competence). Finally, changes in maladaptive strategy catastrophism were also observed in the group without depressive symptoms. These results are consistent with previous studies which show that training in mindfulness affects coping styles related to perspective and judgement (Zenner et al., 2014). People dissociate certain emotions because they consider them threatening. This dissociation makes building a complete reality difficult and favors the presence of

Table 3. Univariate Comparisons in Depressive Symptomatology, Coping, and Metacognitive Skills

	Waiting list		Pre-test		Post-test		3-month follow-up		Г	2
	М	SD	М	SD	М	SD	М	SD	r	η²
Depressed affect	5.37	4.27	6.25	5.20	4.12	2.96	5.87	3.32	1.69	.10
Positive affect	$3.18^{3,4}$	2.16	3.31	2.33	9.50^{1}	1.50	3.25^{1}	1.84	44.47*	.74
Somatic and retarded activity	4.25	2.72	5.00	2.80	4.12	1.62	4.62	2.24	0.62	.04
Interpersonal difficulties	1.31	1.30	1.81	2.66	0.875	0.806	1.37	1.02	0.91	.05

Note. ¹Differences between the score in this phase and the score in the waiting list according to the Bonferroni's post hoc test; ¹waiting list; ²pre-test; ³post-test; ⁴3-month follow-up.

^{*}p < .01.

 $[\]hat{p}$ < .001.

Table 4. Univariate Comparisons in Depressive Symptomatology, Coping, and Metacognitive Skills

	Waiting	ng list Pre-tes		est Post-test		test	3-month follow-up		Г	2
	M	SD	М	SD	M	SD	М	SD	Γ	η^2
Self-blame	4.932,3,4	2.05	4.53 ¹	1.36	4.731	1.67	4.871	2.03	13.44***	.49
Acceptance	7.733,4	2.25	7.00	1.65	8.00 ¹	0.65	8.471	1.51	14.45***	.51
Rumination	6.80	1.93	6.00	1.93	6.67	1.23	7.00	1.69	1.02	.07
Positive refocusing	5.47	1.92	4.534	1.77	5.40	1.76	6.33 ²	1.34	3.76*	.21
Planification	7.67	1.04	7.67	1.71	7.80	1.01	8.47	1.73	1.13	.08
Positive appraisal	7.60	1.72	7.20^{4}	1.93	8.33	1.50	8.872	1.30	3.85*	.22
Putting into perspective	7.73	1.94	6.00^{3}	2.20	8.072	1.39	7.80	1.47	4.77**	.25
Catastrophizing	4.47	2.29	4.73 ³	2.12	3.20^{2}	1.57	4.13	1.46	3.87*	.22
Other-blame	4.13	2.00	4.13	1.81	3.73	1.58	4.07	1.49	0.34	.02

Note. ¹Differences between the score in this phase and the score in the waiting list according to the Bonferroni's post hoc test; ¹waiting list; ²pre-test; ³post-test; ⁴3-month follow-up.

appraisals at the mercy of emotional state (Hargus, Crane, Barnhofer, & Williams, 2010). When people stop fighting against the idea of what they should feel and let emotions arise, they can read their/others' feelings more clearly, improving relational communication and creating a wider story of themselves (Safran & Muran, 2005). As mental contents are not dissociated and vision of their mental states is global and not biased, these people may show an increased ability to put any kind of mental contents into perspective. This increase of consciousness may be related to the gain in the ability to decenter.

Results regarding the effect of the mindfulness intervention in metacognitive variables have shown a significant improvement in the ability to observe (mindfulness) and the ability to decenter both in the total group and in the group with depressive symptoms. Meanwhile, in the group without depressive symptoms results show greater improvement over the other two groups showing changes in variables of mindfulness (observe, describe, no judgment) and decentering. These results show that the intervention in mindfulness improves certain metacognitive skills and are consistent with some studies indicating increases in decentering after mindfulness intervention (Bieling et al., 2012; Getch et al., 2014; Hargus et al., 2010).

Finally, a comparison of changes in each group (presence/absence of clinically significant depressive symptoms) shows that the effect of the intervention is higher in the group with depressive symptoms. However, the improvement in "describe" and "no judgement" meta-cognitive skills is bigger in the group without depression. These results are consistent with previous studies showing how mindfulness interventions in people with mindfulness disposition have a greater increase compared to those with lower rates in these capacities (Shapiro et al., 2011).

These results allow us to consider mindfulness training as a possible tool for reducing long-term depressive symptoms. Also, being a group and short-term (2 months) intervention makes this technique a low cost and effective tool for complementary treatment in emotional disorders.

Nevertheless, this study is not exempt from limitations. The lack of a comparison group in which other technique was used does not let us compare the effectiveness of mindfulness based interventions with other techniques. Secondly, there was no clinical sample and the sample size is not very high. Therefore, it would be interesting to conduct further studies with clinical samples. Also, there were differences in sociodemographic characteristics between two ad-hoc groups and the size of the sample. Thirdly, depressive symptoms were measured with one instrument only. Although it is a screening instrument, further tools should be used for assessment. Future studies should be oriented towards the study of long term effects of mindfulness interventions and its comparison with other techniques.

Conflict of Interest

The authors of this article declare no conflict of interest.

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