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The feasibility of aromatherapy massage to reduce symptoms of Idiopathic Environmental Intolerance: A pilot study

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## **Abstract**

**Objectives:** Idiopathic Environmental Intolerance (IEI) is an acquired disorder with multiple recurrent symptoms, which is associated with diverse environmental factors that are tolerated by the majority of people. IEI is an illness of uncertain aetiology, making it difficult to treat using conventional medicine. Therefore, there is a need for novel therapies to control the symptoms of IEI. The objective of this study was to evaluate the feasibility and impact of aromatherapy massage for individuals with IEI.

**Design:** Non-blinded crossover trial

**Setting:** IEI patients who attended a clinic in Sapporo city were recruited, and sixteen patients were enrolled. Participants were clinically examined by an experienced medical doctor and met the criteria included in the working definition of IEI disorder.

**Interventions:** During the active period, participants received four one-hour aromatherapy massage sessions every two weeks. During the control period, the participants did not receive any massages.

**Main outcome measurements:** Scores on the IEI-scales trigger checklist, symptoms, life impact, and the State Anxiety Inventory were assessed before and after each period. Short-term mood enhancement was evaluated using the Profiles of Mood Status (POMS) before and after sessions.

**Results:** Due to period effects, evaluation of the results had to be restricted to the first period, and the result showed no effect of intervention. All six sub-scales of the POMS improved after each session. (mean score differences: 4.89 to 1.33,  $p < 0.05$ ).

**Conclusions:** Aromatherapy was well tolerated by subjects with IEI; however, aromatherapy, as applied in this study, did not suggest any specific effects on IEI condition.

## Introduction

Idiopathic Environmental Intolerances (IEI) or Multiple Chemical Sensitivity (MCS), which was first reported in 1987 by Cullen,<sup>1</sup> is an illness that causes a person to be extremely affected by a low level of certain chemicals. IEI is considered by the World Health Organization and the International Programme on Chemical Safety (Berlin 1996)<sup>2</sup> to be a more accurate descriptor of the condition, and a working definition of this disorder is as follows: (1) IEI is an acquired disorder with multiple recurrent symptoms; (2) it is associated with diverse environmental factors that are tolerated by the majority of people; and (3) it is not explained by any known medical or psychiatric/psychological disorder. In the United States, the prevalence rate of self-reported IEI is 11.2-12.3%, while that of clinician-diagnosed IEI or environmental illness is 6.3%.<sup>3-5</sup> The prevalence of self-reported IEI is 9.0% in Germany,<sup>6</sup> while the potential prevalence of IEI is 0.7-2.0% in Japan.<sup>7</sup> Patients with IEI report a variety of symptoms, including fatigue, anxiety, headaches, insomnia, lack of concentration, or depression without physical signs or abnormalities on biomedical tests.<sup>6-11</sup> Although the prevalence of IEI varies due to the different definitions of the condition, the estimated number of people suffering from IEI cannot be ignored.

IEI is not a clinically defined disease, as there are neither accepted theories of its underlying mechanisms nor validated clinical criteria for diagnosis. There are several studies underway to determine the aetiological source of IEI. Genetic polymorphisms in drug-metabolising enzymes have previously been examined;<sup>12, 13</sup> however, genetic involvement in IEI remains unclear. Experimental exposures to various chemicals,<sup>12-15</sup> as well as studies of groups at high risk for

chemical exposures,<sup>16</sup> have also failed to identify any differences between IEI patients and control subjects. Thus, the hypothesis that frequent chemical exposure causes an increased risk for developing IEI has not yet been confirmed. However, IEI and panic disorders share a common neurogenetic basis<sup>8</sup> and show a similar sensitivity response to carbon dioxide inhalation.<sup>17</sup> Thus, the anxiety-producing effects of IEI symptoms and its psychological profile have been considered,<sup>18-20</sup> and several researchers have reported IEI to be a subgroup of somatoform and panic disorders. Another recent hypothesis is that IEI is a conditioned, negative emotional response to unpleasant odours.<sup>21</sup> Many IEI patients have reported reactions to behavioural disruptions in daily activities by odorous substances. The emotional response to odours and its conditioned reflexes can influence mood, cognition, and behavior.<sup>22</sup>

Even if the aetiologies for IEI remain controversial and unknown, individuals with IEI still need assistance with their symptoms.<sup>23</sup> Because there is no clinically validated treatment for IEI, the ideal therapy would be one that controls symptoms but is not dependent on a specific organic diagnosis or aetiology.<sup>23</sup> On occasion, IEI patients seek unorthodox therapies, such as sublingual neutralisation or various “detoxification” treatment programmes, even if they are costly and lack efficacy.<sup>24</sup> Several treatment recommendations for IEI, such as behavioural modification approaches, have been discussed;<sup>25</sup> however, none has been examined scientifically.

Meanwhile, odour-emotion associations have been used to increase patients’ comfort and reduce anxiety. This therapy is called aromatherapy, and it has become one of the most popular complementary therapies used in this disorder, especially in the UK. Aromatherapy has anecdotally

been used to reduce anxiety, depression, pain, fatigue, and nausea. To date, the evidence for aromatherapy is scarce. However, this therapy has been noted to have positive effects on the autonomic nervous system<sup>26</sup> and the immune system;<sup>27, 28</sup> in addition, aromatherapy has been noted to improve mood <sup>27, 28</sup> and reduce anxiety or depression among cancer patients,<sup>27-29</sup> postpartum mothers,<sup>30, 31</sup> and dementia patients<sup>32</sup>. Because fatigue, anxiety, and depression are the primary symptoms reported by patients with IEI,<sup>6, 9, 11, 33</sup> our hypothesis is as follows: due to its pleasant odours, aromatherapy enhances positive emotions in patients with IEI, and positive emotions may mask the patients' conditioned physiological and/or psychological reflexes to stressful odours, thereby offering symptom relief. In contrast, perfume is one of the leading trigger substances to provoke IEI symptoms,<sup>9, 34</sup> thus, the acceptability of aromatherapy for IEI patients is questionable. Therefore, the objective of this study was to evaluate the efficacy of aromatherapy in reducing the symptoms of IEI. The specific aims of this pilot study were (1) to determine whether aromatherapy is acceptable for use in IEI and (2) to determine whether aromatherapy reduces the symptoms of IEI.

## **Methods**

A non-blinded crossover trial was used to evaluate the effect of aromatherapy massage on patients with Idiopathic Environmental Intolerance. The study was registered in the University Hospital Medical Information Network-Clinical Trial Registry (UMIN-CTR) (Tokyo, Japan) UMIN000003998.

## **Subjects**

Twenty-six adult outpatients were recruited who felt that they may suffer from IEI and who had visited the primary care clinic to see a physician who specialised in paediatrics, allergy, Sick Building Syndrome, and IEI in Sapporo city, Japan from September 2007 to December 2008. The inclusion criteria are those who met the working definition of the IEI disorder.<sup>2</sup> A clinical examination was performed by an experienced medical doctor in this field. In addition, the Chemical Odour Sensitivity Scale<sup>19</sup> was used to screen patients, and patients who scored above 26 for men and 30 for women were included. Patients who did not consent or who planned to move or renovate their home during the upcoming six months were excluded. We also assessed patients to determine whether they were allergic to the massage oil used in the study or whether their symptoms were provoked by the smell of the oil; this assessment was done prior to inclusion in the study. A closed patch test<sup>39</sup> was performed prior to the intervention to confirm that the participants did not have an allergic reaction to the massage oil. A total of 15 µl each of the massage oil and the physiological salt solution (Otsuka Pharmaceutical Co., Ltd, Tokyo, Japan), which served as a negative control, was dropped onto a Fin Chamber© (Epitest LTD Oy, Tuusula, Finland) and taped to the forearm of the participants using Scanpor® tape (Alpharma AS, Norway). Self-inspection of the reaction to the massage oil was reported after 24 hours. After providing written informed consent, the subjects were randomly assigned to group A or B using a random number sequence and were subsequently stratified by gender and age (20-34/35-49/50+) into randomly sized blocks. Group A received aromatherapy sessions during the first period and then switched to the control period for two months, and group B received the opposite.



The sample size was calculated based on the State Anxiety Inventory (SAI) score,  $50.9 \pm 13.6$  (mean $\pm$ SD), among Japanese IEI subjects reported by Tonori et al. (2001)<sup>35</sup>. SAI scores below 40 for men and 42 for women are considered to be normal<sup>36</sup>. The sample size required for a mean difference of 7.64 (15%) with an  $\alpha=0.05$  and  $\beta=0.02$  was  $n=36$  in each group. Perfume is one of the primary trigger substances for provoking IEI symptoms; therefore, it was unclear whether IEI patients could tolerate an aromatherapy intervention. In addition, IEI patients report a variety of symptoms<sup>6-11</sup>, thus for the pilot study, we chose a non-blinded crossover trial in which aromatherapy was given to all of the participants on a randomised crossover basis, despite the limitation of the absence of blinding.

## **Measurements**

The chemical odour sensitivity scale (COSS) is an 11-item scale that assesses physical responses (0=not at all to 4= very strong) to the odours of common environmental chemicals. The ideal cut-off point for screening was previously described as 26 for men and 30 for women.<sup>19</sup> To evaluate the effect of the intervention, the IEI-scales were used as a preliminary outcome. The IEI-scales consist of three subscales: Trigger checklist, Symptoms, and Life Impact.<sup>37</sup> The trigger checklist assesses how strongly each of 15 environmental substances cause adverse reactions; the scale ranges from 0 (not at all) to 4 (very strong), with total scores ranging from 0 to 60. The symptoms assessed the presence (1) or absence (0) of 20 complaints due to exposure to environmental substances, as listed in the Trigger checklist. Total symptoms ranged from 0 to 20. The life Impact subscale indicates

how much the participants feel that their life is impaired as a result of their hypersensitivity to odours or chemicals. Each item is scored from 0 (not at all) to 4 (very strong), with a total score on 15 items ranging from 0 to 60. Both the COSS and IEI-scales questionnaires were translated into Japanese. Changes in self-reported anxiety was assessed using the Japanese version of State Anxiety Inventory (SAI) Form Y (STAI-JY).<sup>36</sup> The IEI-scale and SAI scores were measured before and after each period.

To assess the immediate effect of aromatherapy, the participants were asked to complete the Profiles of Mood Status (POMS) before and after each session.

All measurements were completed by the participants.

## **Interventions**

Essential oils of Melissa (*Melissa officinalis* Lot.MOH1), Juniper (*Juniperus communis* LOT. JCB2), and Rosemary (*Rosmarinus officinalis* ct. cineol LOT.BIOROSF2PH0705) were purchased from Pranarom International (Ghislenghien, Belgium) and mixed into Jojoba oil (*Simmondsia sinensis*) (Kensoigakusha Co. LTD, Tokyo, Japan) at a ratio of 1:2:2 as a 1% solution (hereafter described as the massage oil). Melissa is anecdotally used for anxiety, depression, migraine, and shock<sup>38</sup>; thus, it was expected to relieve participants' stress. Rosemary is anecdotally used for detoxification and poor circulation<sup>38</sup>; thus, it was expected to stimulate nervous and mental activities. Juniper was selected for its diuretic properties and its synergetic effects with Rosemary<sup>38</sup>, the goal being to eliminate any chemicals that the participant believed to be harmful. During each session, 20 to 30 ml of the

massage oil was applied, and the remaining oil was given to the participants for daily use.

During the active period, participants received four aromatherapy massage sessions every two weeks. Aromatherapy massage of the back, shoulders, arms, hands, lower legs and feet was given by two qualified therapists from the International Federation of Aromatherapists (London, UK). To standardise the massage, therapists were trained for 30 hours. All four sessions were received from the same therapist at the same venue. During the control period, all participants went about their daily lives without aromatherapy massage.

### **Chemical exposure levels at home**

To assess the indoor chemical exposure levels at home, monitoring of aldehydes, acetone and volatile organic compounds (VOCs) was carried out in the living room of the patients' homes. Air samples from 100–150 cm above the floor were collected for 24 hours with Supelco DSD-DNPH and VOC-SD samplers (Sigma-Aldrich, St. Louis, MO, USA) for aldehydes, acetone and VOCs. Formaldehydes and acetone were quantified via high-performance liquid chromatography equipped with an ultraviolet detector (Hitachi D-7100, Hitachi Ltd., Tokyo, Japan), and 27 VOCs were quantified using gas chromatography/mass spectrometry (Hewlett Packard 630N/MSD) (Hewlett Packard Co., CA, USA) using a previously described method.<sup>40, 41</sup> Total VOCs (TVOCs) were calculated as the sum of all VOCs, and VOC values under the limit of detection (LOD),  $0.5 \mu\text{g}/\text{m}^3$ , were considered to be half of the LOD. All analyses were performed at the Osaka Occupational Health Service Centre, Japan Industrial Safety and Health Association (Osaka, Japan)

## **Data analysis**

Demographic data of the two groups were compared using Pearson's chi-square test. Score differences were calculated by subtracting the score prior to the intervention from that after the active/control period for each participant, and therefore, negative value means improvement. Score differences were analysed using t-test for between groups for each period separately, and paired t-tests for within each group separately. The effect size of Cohen's  $d^{42}$  was calculated for each variable using a standardised mean difference based on the mean values before and after the intervention. To examine the short-term efficacy of aromatherapy massage, pre- and post-aromatherapy POMS were analysed via repeated measured analysis of variance (ANOVA). All statistical calculations were performed using the Japanese version of the Statistical Program for Social Sciences 14.0J (SPSS Inc., Chicago, IL, USA) for Windows.

## **Ethics**

The study protocol was approved by the ethical board for clinical studies at Hokkaido University Graduate School of Medicine. This study was conducted after obtaining the written informed consent of all participants.

## **Results**

The progression of the trial and the numbers of participants are shown in Figure 1. Sixteen patients

were involved in the study, and all participants completed four aromatherapy sessions and questionnaire surveys.

Participants included one male, and the mean age  $\pm$  standard deviation (SD) was 46.1 $\pm$ 8.2.

Characteristics of the participants are shown in Table 1. None of the factors showed statistically significant differences between the two groups. Two participants were currently taking medication for hypertension, and one participant was taking medication for allergic conjunctivitis, asthma, hay fever, food allergy panic disorder, and depression (data not shown). Four patients were taking psychotropic drugs, including benzodiazepines, rilmazafone hydrochloride or serotonin and norepinephrine reuptake inhibitors. Two subjects took psychotropic drugs for the entire study period, while two others took psychotropic drugs during only the control period.

Mean scores  $\pm$  SD for the IEI-Scales and SAI score differences changes during active and control periods depending on the order of treatment administration are shown in Table 2. Cohen's *d* is represented in absolute value. However, in the group received aromatherapy during the 1st period showed increasing SAI score in both active and control periods with larger difference in active period means scores got worse during the active period. Also during the first period, SAI score increased in both groups with larger difference in Aromatherapy group. There was no score difference between the active and control periods on any of the scales for both groups. According to Cohen's guidelines<sup>42</sup>, the effect sizes of our interventions were small to large with respect to change in the IEI subscales and the SAI scale. Figure 2 shows the short-term effects of intervention compared using the POMS pre- and post-aromatherapy. There were significant improvements in all

of the six subscales of POMS post-aromatherapy.

Data concerning major chemical levels at the subjects' homes are shown in Table 3 in combination with a result from a previous study<sup>40</sup> as a reference. Levels of p-dichlorobenzene and total VOCs exceeded safe threshold values in indoors guided by the Ministry of Health, Labour and Welfare, Japan at one home each. Although there are no set guidelines for acetone, a relatively high level was determined at one home. The levels of other chemicals, including formaldehyde, were relatively low at subjects' homes.

There were two reports of adverse events after aromatherapy session, which included one report of headache and one incident of urticaria. The causal relationship between aromatherapy and these events was not clear. Because the events were not severe, both participants wanted to continue the study and completed the four interventions.

## **Discussion**

This study is the first preliminary study to examine an aromatherapy intervention among patients with IEI. The major findings of the study are as follows: (1) aromatherapy was well tolerated by IEI patients, (2) each aromatherapy session provided mood improvement as an immediate effect. During second period, IEI-symptoms and Life Impact scores reduced in Aromatherapy group. However, among group B, which is the group that had the control period prior to the active treatment, the score differences of IEI-scales reduced both during control and active period. Symptom burden seems to be less consistently for the group B, and different effect size for group A and B would suggest a period

effect. Thus, the reductions of the scores during second period were not likely to be specific to aromatherapy, and had to limit evaluation to the first period before crossover by discarded second period. There was no score difference on any of the IEI subscales between group A and B at the first period, and between the active and control periods for both group A and B. Therefore, aromatherapy as applied in this study failed to relieve symptoms of IEI.

One strength of the study was the lack of participant withdrawal and the 100% completion rate of all participants, although the number of participants was notably small. The results suggest that aromatherapy is acceptable for patients with IEI and that it improves mood in the short-term, but that the observed improvements are likely to be non-specific and not attributable to aromatherapy. Gibson et al.<sup>43</sup> examined self-reported perceived treatment efficacy in 916 IEI patients; these researchers found that 60% of participants receiving body therapy found it to be helpful. The results of this study confirm the acceptance of aromatherapy among IEI patients. However, the number and interval of sessions was not suitable for maintaining a positive mood. According to interviews at the end of the study period, 50% of the subjects reported that a biweekly interval was too long, and 75% reported that four sessions were not enough. An aromatherapy intervention would likely yield better results in IEI patients if the intervals were shortened and if the number of sessions was increased.

Although we recruited participants from only one clinic and the sample size of our study was small, the characteristics of the participants in this study were consistent with that of previously reported IEI patients; thus, our sample was representative of IEI patients. The prevalence of IEI is high among middle-aged populations, and 70-80% of patients are female.<sup>44, 45</sup> The study included

only one male. Kiecolt-Glaser et al.<sup>46</sup> reported that olfactory influences do not differ between genders; thus, the data from the one male subject were included in the results. Bailer et al.<sup>37</sup> reported that mean scores for the IEI trigger checklist, symptoms and life impact subscales were approximately 33, 10, and 27, respectively.<sup>37, 47</sup> Baseline scores for each subscale were similar to that obtained in Bailer's study. Among Japanese adult workers, the mean score on the Trait Anxiety Inventory (TAI) was 43,<sup>36</sup> whereas baseline TAI scores in this study were approximately 49 (data not shown). Higher TAI scores for IEI patients compared to normal subjects are consistent with a report by Tonori et al.,<sup>35</sup> who described the sustained high anxiety levels among IEI patients. Patients taking psychotropic drugs at baseline were less likely to have improvements in anxiety;<sup>29</sup> thus, including this group in the analysis may have resulted in a ceiling effect and little room for additional improvement neither during the aromatherapy period nor during the control period. The result when the four subjects who took psychotropic drugs were excluded from analysis showed a similar trend; therefore, we included all participants in the analysis of the data.

In this study, all subjects received the same aromatherapy intervention, which included a fixed amount of blended oil and the same number of massages in a fixed sequence. To examine the effect of aromatherapy, some studies have applied aromatherapy using a package with a selection from various essential oils that can be applied in various ways. One study included 20 essential oils, and the therapist tailored the oil blends and practice to each individual.<sup>29</sup> In another study, one of the five essential oils was used with several different modes of application, including massage, footbath, taper, and compression<sup>48</sup>. Such variations may reflect the real-world practice of



aromatherapy; however, it is difficult to generalise the effects from such results, as it is not possible to evaluate which essential oils or methods of application were effective. Melissa combined with Valerian treatments have been reported to reduce laboratory-induced stress and are effective treatments for restlessness and dyssomnia.<sup>49, 50</sup> In this study, the products were given orally. Ballard et al.<sup>32</sup> applied Melissa topically in patients with dementia and found it was effective in managing agitation and quality of life. Inhalation of rosemary oil has been reported to reduce stress and anxiety.<sup>49</sup> The immediate effect of aromatherapy was assessed, and a significant improvement in SAI was reported<sup>29</sup>. Takeda et al. concluded that aromatherapy is more advantageous with respect to psychological or subjective evaluations but not physiologic ones.<sup>51</sup> In this study, the results show a statistically significant improvement in short-term mood, which is consistent with findings from previous studies. As aromatherapy causes a short-term improvement in stress among patients with IEI, the next goal is to sustain a positive reaction and control symptoms.

There are several limitations to this study. The largest weakness of the study was the small sample size and non-blinded crossover trial design. We were unable to collect the calculated sample size of participants, due to time constraints. The small sample size was not sufficiently powered for a robust statistical analysis. Although participants' characteristics did not differ between the two groups at baseline, the sequence in which participants experienced the active and control periods may have biased the results. All participants were told that they were receiving aromatherapy and the study was unable to control for the patient's condition over time. Lastly, COSS and IEI-scales were translated from German to Japanese by a professional translator;

however, back translation from Japanese to German was not conducted.

Concentrations of indoor chemicals in the subjects' homes were similar to slightly lower than previous surveys in Sapporo.<sup>40</sup> Saito et al. compared differences in exposure levels to chemicals between MCS (IEI) patients and controls; levels of exposure to formaldehyde, acetaldehyde and p-dichlorobenzene were significantly lower for MCS cases.<sup>52</sup> IEI patients may intentionally try to avoid chemical exposure. Meanwhile, acetone or p-dichlorobenzene levels exceeded the safe threshold values in indoors in the homes of two of the subjects in the study. Because participants did not complain of any symptoms at home, these chemicals may not have been agents that provoked symptoms. One study using a single-blind chemical exposure test for IEI showed that seven out of eleven participants had negative results, i.e., they either had no symptoms or had symptoms prior to the stimulus.<sup>53</sup> The authors concluded that complaints of symptoms prior to provocation may be induced by fear of the chemicals themselves.

Most of the subjects in this study reported that the smell of the perfumes was intolerable. Thus, it is interesting that the subjects accepted the aromatherapy intervention, despite the fact that the essential oils used for massage were an aggregation of "chemicals". These results support the hypothesis that the symptoms of IEI are conditioned emotional responses to chemicals. In one study, participants who had been given warning about environmental pollution reports in advance of a chemical exposure challenge reported more symptoms for both ammonia (foul-smelling) and niaouli (natural, pleasant-smelling).<sup>54</sup> Although the subjects in the study were healthy volunteers, similar beliefs about chemical substances could facilitate the conditioning of symptoms in response to

odorous chemicals. Guppa et al.<sup>55</sup> suggested that the treatment preferences of patients with IEI and the general beliefs about chemicals may enhance outcomes and should potentially be the target of any intervention. Essential oils are natural (non-chemical) perfumes arising from nature, as opposed to manmade synthetic chemicals, which may have affected the results. The aetiology of IEI is still unknown, making this condition difficult to treat using conventional medicine. In this study, IEI participants' beliefs that the essential oils have a natural and pleasant odour may have improved their mood, at least in the short-term.

## **Conclusion**

In this preliminary study, the aromatherapy intervention was well tolerated by IEI subjects. However, there was no reduction on the IEI-scales and SAI suggested that aromatherapy, as applied in this study, did not show any effects in the management of IEI.

## **Conflict of interest**

None.

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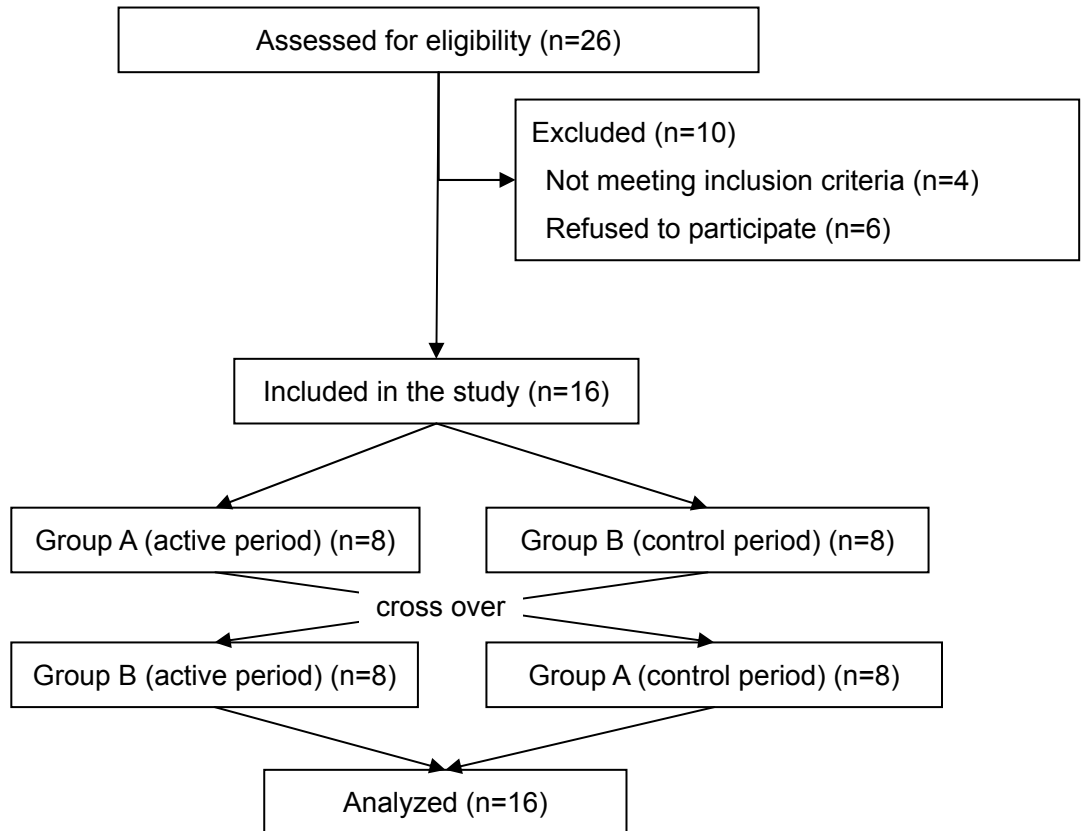
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## Figure legends

Figure 2. Each bar shows mean+SD scores of average of four aromatherapy sessions for each subject. Light bars indicate pre- and dark bars indicate post- sessions. P values were calculated with repeated measures of ANOVA.

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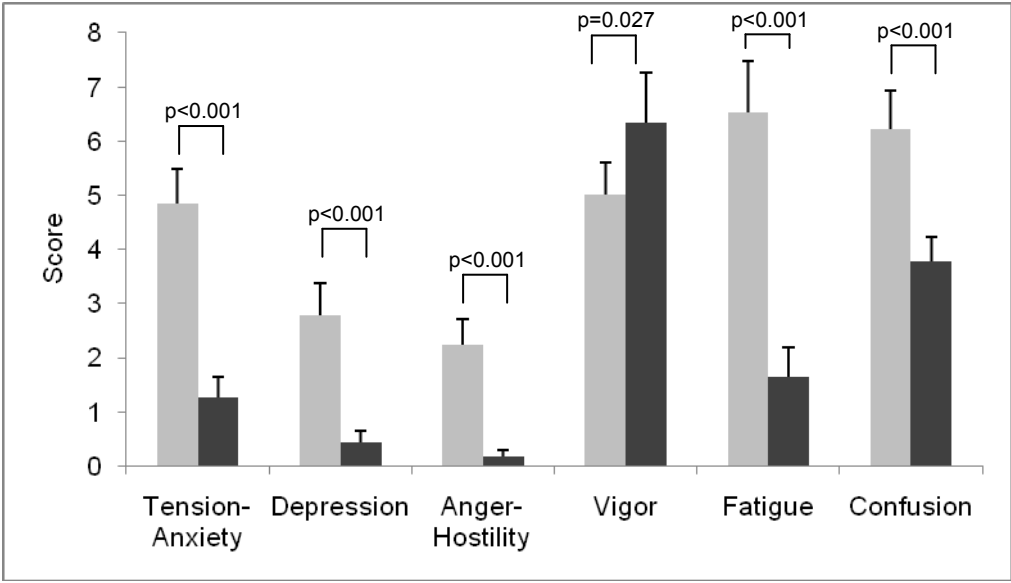
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Figure 1: Flow diagram



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Figure 2: POMS score pre- and post-aromatherapy (N=16)

Table 1: Characteristics of the participants

		Total (N=16)	Group A (N=8)	Group B (N=8)
Gender:	Female/Male	15/1	7/1	8/0
Age :	Mean $\pm$ SD	46.1 $\pm$ 8.2	45.3 $\pm$ 7.1	47.0 $\pm$ 9.6
Occupation	Full time	5	4	1
	Part time	4	2	2
	House Wife	7	2	5
Educational level	Less than 12years	10	4	6
	13-15 years	5	4	1
	16 years +	1	0	1
Marital Status	Married	12	5	7
	Single	3	2	1
	Divorce/Widow	1	1	0
Number of family	None	3	2	1
	1	6	3	3
	2-3	5	2	3
	4+	2	1	1
Duration of sleep	Less than 6 hours	5	2	3
	More or equal to 6 hours	11	6	5
Alcohol intake	None	11	4	7
	Sometime	4	3	1
	Everyday	1	1	0
Regular exercise	Yes	6	3	3
	No	10	5	5
Current Smoking	No	12	5	7
	Yes	4	3	1
Breakfast	Every morning	13	8	5
	Sometimes	2	0	2
	never	1	0	1
Well balanced diet	Yes	10	4	6
	Sometimes	4	2	2
	No	2	2	0
Psychotropic drug usage	Yes	4	2	2
COSS score	Mean $\pm$ SD	42.3	42.5 $\pm$ 8.6	42.0 $\pm$ 7.9
		(range 30-53)		

Table 2: IEI-Scales and SAI score differences changes during active and control periods depending on the order of treatment administration

		Aromatherapy during the 1st period (Group A)			Aromatherapy during the 2nd period (Group B)			Between groups	
		Score differences	<i>P</i> <sup>a)</sup>	Effect size <sup>b)</sup>	Score differences	<i>P</i> <sup>c)</sup>	Effect size <sup>d)</sup>	<i>P</i> <sup>e)</sup>	Effect size <sup>f)</sup>
First period (before crossover)	IEI-Trigger (0-60)	1.9±9.6			-6.5±12.2			n.s	0.77
	IEI-Symptoms (0-20)	-2.4±3.1			-2.8±2.5			n.s	0.14
	IEI-Life Impact (0-60)	-6.0±8.6			-11.9±14.6			n.s	0.49
	SAI (20-80)	8.3±10.0			3.0±11.8			0.026	0.48
Second period (after crossover)	IEI-Trigger (0-60)	3.4±8.9	n.s.	0.87	-6.1±13.1	n.s.	0.40	n.s	0.85
	IEI-Symptoms (0-20)	1.6±2.8	n.s.	0.05	-0.8±5.1	n.s.	0.22	0.004	0.58
	IEI-Life Impact (0-60)	3.0±6.2	n.s.	1.44	-3.8±6.4	n.s.	0.68	0.006	1.08
	SAI (20-80)	2.3±4.3	n.s.	0.19	-9.2±13.3	n.s.	0.83	n.s	1.16

Mean ± S.D.

IEI-scales and SAI score differences were calculated by subtracting the score prior to the intervention from that after the active/control period for each participant, and negative value means improvement.

<sup>a)</sup> P-values were calculated with paired t-test to compare scores between first period and second period in the group received aromatherapy during the 1<sup>st</sup> period (Group A)

<sup>b)</sup> Effect sizes (Cohen's d) were calculated as  $d = \frac{|\text{mean}_{\text{Active period}} - \text{mean}_{\text{Control period}}|}{\sigma}$  in the group received aromatherapy during the 1<sup>st</sup> period (Group A)

<sup>c)</sup> P-values were calculated with paired t-test to compare scores between first period and second period in the group received aromatherapy during the 2<sup>nd</sup> period (Group B)

<sup>d)</sup> Effect sizes (Cohen's d) were calculated as  $d = \frac{|\text{mean}_{\text{Active period}} - \text{mean}_{\text{Control period}}|}{\sigma}$  in the group received aromatherapy during the 2<sup>nd</sup> period (Group B)

<sup>e)</sup> P-values were calculated with t-test to compare scores between the group A and B for each (first/second) period

<sup>f)</sup> Effect sizes (Cohen's d) were calculated as  $d = \frac{|\text{mean}_{\text{Active}} - \text{mean}_{\text{Control}}|}{\sigma}$  between the group A and B for each (first/second) period

n.s.: not significant

Table 3: Concentrations of chemicals at home

	Median	(Range)	Median 104 single family dwellings in Sapporo Takeda et al.2009	Safe threadhold values in indoors guided by Ministry of Health Labour and Welfare, Japan
Formaldehyde	28.2	(7.0-79.4)	63.6	100
Acetaldehyde	19.4	(<LOD-53.9)	34.3	48
Acetone	34.7	(5.8-535.1)	41.4	-
Toluene	13.4	(4.1-43.5)	18.7	260
Ethylbenzene	4.7	(<LOD-25.8)	4.6	3800
Styrene	<LOD <sup>b)</sup>	(<LOD-0.7)	<LOD	220
Xylene	16.7	(1.8-114.0)	11.7	870
p-Dichlorobenzene	26.7	(<LOD-357.7)	<LOD	240
Total VOC <sup>c)</sup>	225.7	(51.1-1307)	142.9	400

Unit:  $\mu\text{g}/\text{m}^3$ LOD is Limit of Detection ( $0.5\mu\text{g}/\text{m}^3$ )