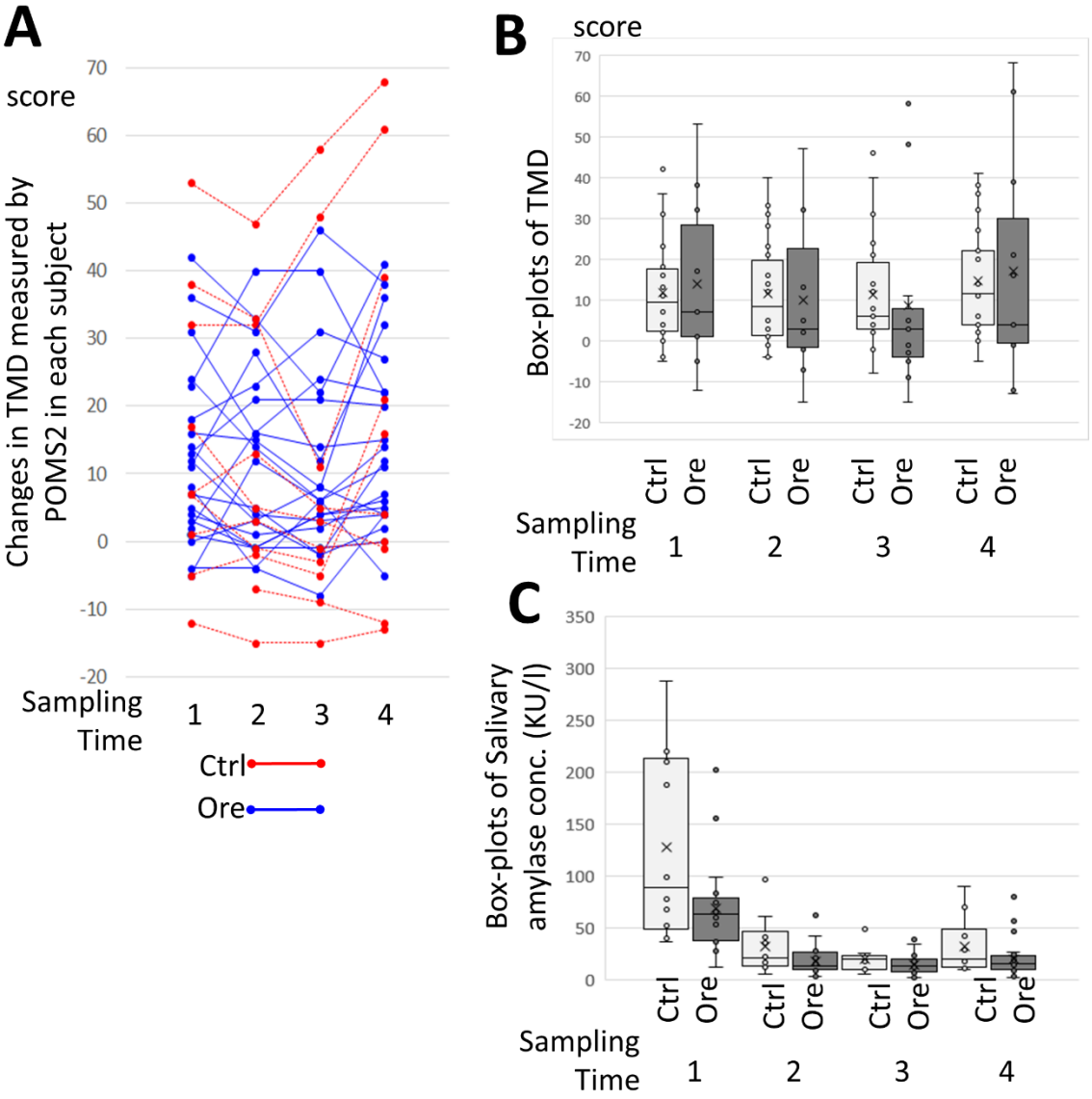


Figure 6. Results of total mood disturbance (TMD) and stress marker. [A] Actual changes in TMD assayed by PPOMS2 in all subjects during sampling times 1 to 4. The red and blue lines indicate NWC (Ctrl) and CCSNOP (Ore) subjects, respectively. A varieties of changes were observed with no regular pattern being observed. [B] Comparison of TMD in NWC (Ctrl) and CCSNOP (Ore) groups at sampling times 1 to 4. There was no significant difference between the two groups. [C] Box-plots show changes in salivary amylase levels (sAmy) as a stress marker in CCSNOP (Ore) and NWC (Ctrl) groups during sampling times 1 to 4. There was no significant difference between the two groups.

Figure 6A shows the changes in TMD as measured by POMS2 in individual subjects. There was no regular pattern observed of changes in TMD. A comparison of CCSNOP (Ore) and NWC (Ctrl) subjects was made and a time-course of the sampling time was assessed. However, no significant changes were observed (Fig. 6B). Additionally, changes in sAmy, employed as a stress marker, are shown in Fig. 6C. Again, no significance changes were observed between CCSNOP (Ore) and NWC (Ctrl) subjects. Although an assessment of the difficulties of everyday life indicated an improvement in CCSNOP subjects, mood and stress markers remained unchanged.

3.3. Specific Ig E and eosinophils

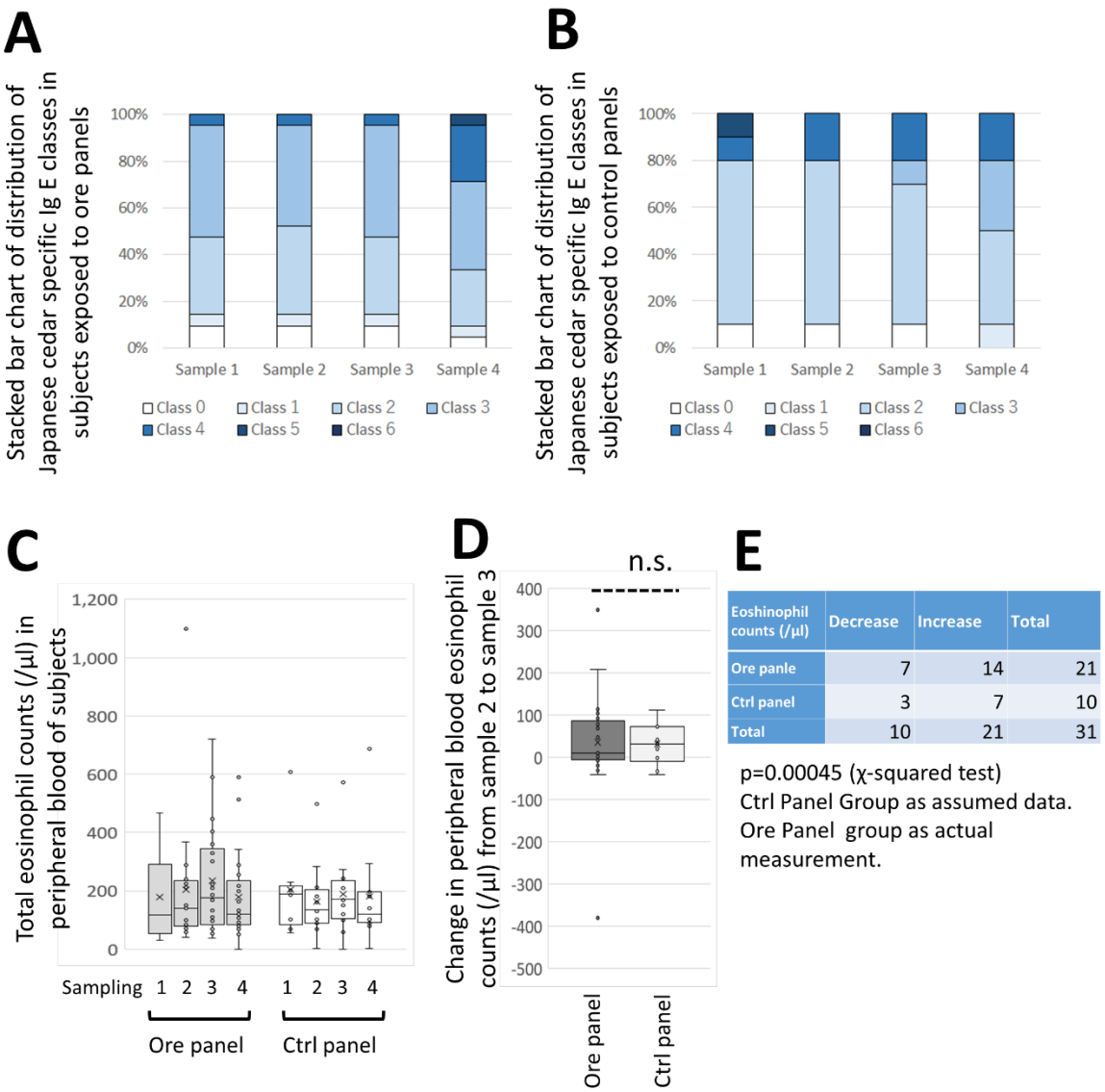


Figure 7. Changes in cedar pollen specific Ig E and eosinophils. Stacked bar charts showing the distribution of Japanese cedar specific Ig E classes 0 to 6 among [A] CCSNOP (ore) and [B] NWC (Control) subjects. [C] Box-plots of total peripheral eosinophil counts in CCNSOP (ore) and NWC (Ctrl) subjects during sampling times 1 to 4. There were no significant differences between the two groups. [D] Box-plots of peripheral blood eosinophil counts from sampling times 2 to 3 in CCSNOP (Ore) and NWC (Ctrl) groups. There were no differences found. [E] χ-squared test of subjects who showed an accelerated decrease in peripheral blood eosinophil counts from sampling times 2 to 3. There was a significant difference and the CCSNOP (Ore) group showed an accelerated decrease in eosinophils.

Figure 7A and 7B show a stacked chart distribution of Japanese cedar specific Ig E classes in CCSNOP (Ore panel) and NWC (Control panel) subjects. Class 0 to 6 designations were as given by the BML Ltd. laboratory test. The classes and Ig E titers were as follows: class 0 [< 0.27 IU/ml], 1 [> 0.27 but ≤ 0.5], 2 [> 0.5 but ≤ 1.80], 3 [> 1.80 but ≤ 7.05], 4 [> 7.0 but ≤ 517.35], 5 [>17.35 but ≤ 29.31] and 6 [>29.31]. Samples 1 to 4 represent sampling time 1 (January), 2 (before panel placement), 3

(just before panel removal) and 4 (almost two months after pollen dispersal). There were some differences regarding class distribution between CCSNOP (Fig. 7A) and NWC (Fig. 7B) subjects. The CCSNOP group included a higher class such as class 3 during the entire sampling period. There is a slight increase in class 3 in the control group, whereas no changes were observed in the CCSNOP group at sampling time point 3 (just after panel placement). Additionally, both groups showed an increase in classes at sampling time point 4. The reason why these classes increased when pollen dispersal had ceased remains unclear. However, since both groups showed similar patterns, this pattern was not dependent on the absence or presence of panels.

Figure 7C shows the changes in absolute eosinophil counts in peripheral blood among CCSNOP (Ore) and NWC (Ctrl) groups. There were no significant differences observed in all sampling times within each group as well as between the two groups at individual sampling times. Moreover, the changes in peripheral eosinophil count from sampling time 2 (just before panel placement) to sampling time 3 (two weeks after panel placement) revealed no difference between the two groups (Fig. 7D). However, a χ-squared test to evaluate the number of subjects that showed an increase or decrease from sampling times 2 to 3 indicated that CCSNOP (Ore) subjects showed significantly higher rates of decreasing eosinophil count compared with NWC (Ctrl) subjects (Fig. 7E).

3.4. Cytokine analyses and generation of prediction formula

Twenty-nine types of cytokines were measured using a Luminex 29 Cytokine Plex Kit. Although our previous study examined changes in individual cytokines during stays (with sleeping) under CCSNOP or NWC conditions, in the present study, our aim was to measure these cytokines in an effort to determine whether CCSNOP affected the immune system.

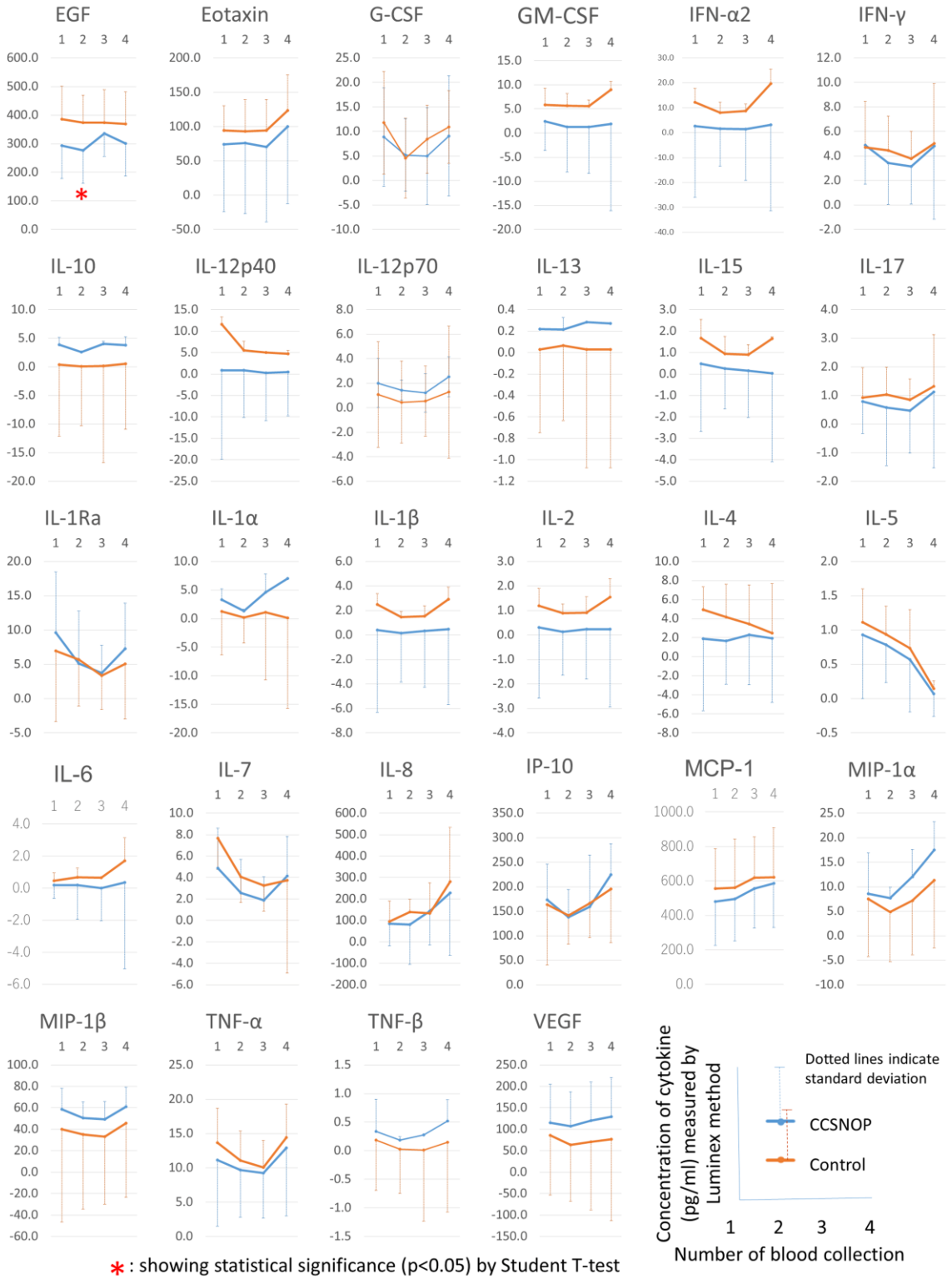


Figure 8. Twenty-eight kinds of cytokines (IL-3 was excluded because it could only be measured with one sample) were measured in four blood collections, and the average value and standard deviation are shown for the CCSNOP and control groups. Moreover, a comparison between each group by Student's t-test revealed that the CCSNOP group showed a higher value than the control group in the first and second blood collection of EGF.

In Fig. 8, 28 types of cytokines were measured in four blood collections, and the average values and standard deviations in the CCSNOP and control groups are

shown. IL-3 was excluded because it could only be measured with one sample. Moreover, a comparison between each group by Student's t-test revealed that the CCSNOP group showed a higher value than the control group in the first and second blood collection of EGF. However, these differences disappeared after the third and fourth blood collections, and we do not consider them to be significant differences in this study.

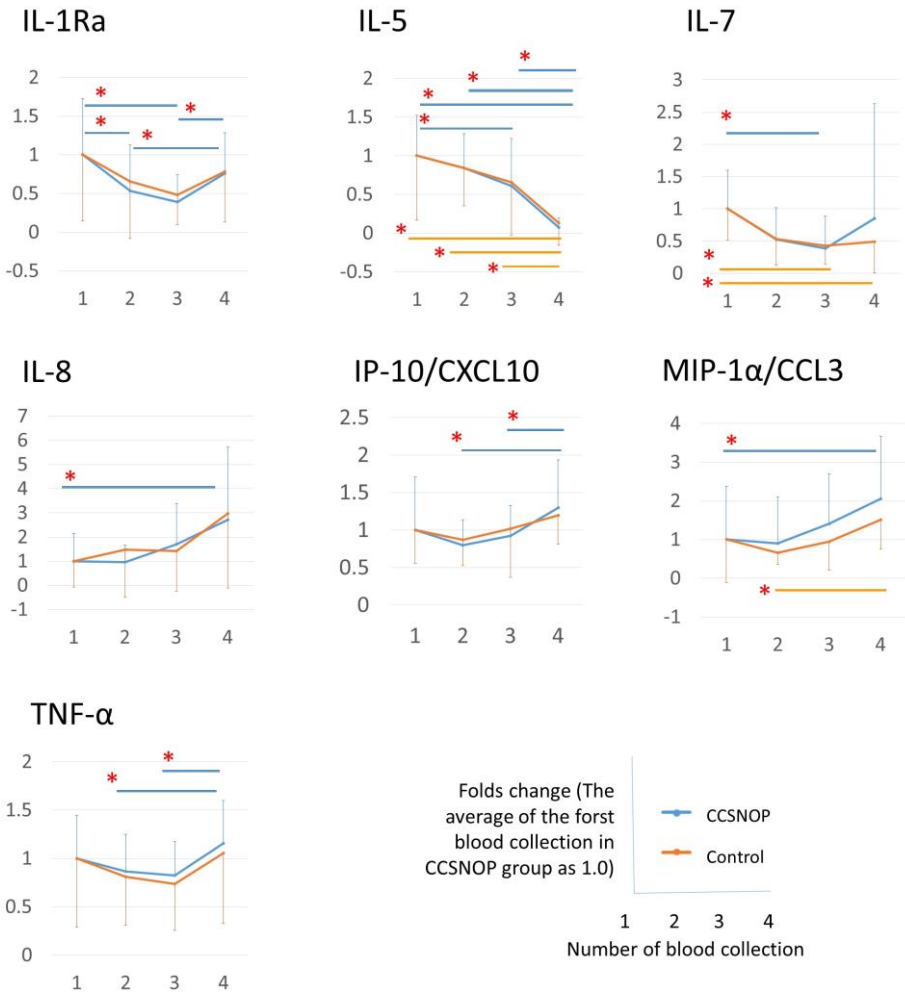


Figure 9. The changes over time of twenty-eight cytokines are shown as a result of examining the relative changes with the average value of the first blood collection in the CCSNOP group as 1.0. Among the twenty-eight cytokines whose real numbers are shown in FIG. 8, seven cytokines that showed a significant difference in the time course of the CCSNOP group or the Control group are shown.

As shown in Fig. 9, with the seven cytokines, changes over time were observed as the results of the first to fourth blood collection in the CCSNOP group or the Control group. However, as shown in Fig. 8, these cytokines are also actually measured, and no difference is observed between the two groups. Also, the significant difference over time may or may not be significant depending on the standard deviation. However, as a whole, both groups showed similar trends.

From the results of Figs. 8 and 9, it was not considered that the improvement in symptoms and medications observed in CCSNOP was the effect of CCSNOP on any single cytokine.

As mentioned above, stays (with sleeping) under CCSNOP conditions for two weeks resulted in a reduction in the severity of symptoms and a decrease in the use of allergy-related medicinals. A formula was generated to predict subjects who stayed under CCSNOP conditions by employing various parameters shown in Fig. 10A that included 28 types of cytokines (IL-3 was omitted since all subjects revealed IL-3 values that were lower than the lower limit of measurement) using multiple regression analysis. All data at sampling time 3 (just after placement of the panels for the 2-week period) were used.

As shown in Fig. 10B, four parameters with constant terms were extracted. Thereafter, the formula generated predicting subjects who stayed under CCSNOP conditions was as follows (also shown in Fig. 10C):

Panel-prediction formula = 0.801-0.061 x GM-CSF (pg/mi)-0.050 x IL-12p40 (pf/ml) -0.004 x Ig G4 (mg/dl) + 0.001 Eosinophil count (/μl)

After generating this formula, the data associated with these parameters for all subjects were substituted into this formula and plotted for CCSNOP (Ore panel) and NWC (Ctrl panel) groups as shown in Fig. 10D. The formula detected with significant difference which panel type each subject was subjected to during the 2-week period. Additionally, as shown in Fig. 10E, the ROC curve highlighted the successful predictive capacity of this formula, with [sensitivity] and [1-specificity] values of 0.905 and 0.100, respectively.

A

Item	Unit	Item	Unit
Background and Diary		Cytokine	
Sex	M/2, F/1	EGF	pg/ml
Medicinals	Used/1, Not-used/0	Eotaxin	pg/ml
Sneeze	1 to 5	GCSF	pg/ml
Runny nose	1 to 5	GMCSF	pg/ml
Stuffy nose	1 to 5	IFNα2	pg/ml
Redness of Eyes	1 to 5	IFNγ	pg/ml
Watery eyes	1 to 5	IL10	pg/ml
Itchy eyes	1 to 5	IL12p40	pg/ml
Everyday life	1 to 5	IL12p70	pg/ml
CBC		IL13	pg/ml
WBC	/μl	IL15	pg/ml
Neutrophil	/μl	IL17	pg/ml
Eosinophil	/μl	IL1ra	pg/ml
Basophil	/μl	IL1α	pg/ml
Monocyte	/μl	IL1β	pg/ml
Hemoglobin	/μl	IL2	pg/ml
Platelet	/μl	IL4	pg/ml
Immunoglobulin		IL5	pg/ml
Ig A	mg/dl	IL6	pg/ml
Ig E	IU/ml	IL7	pg/ml
Ig G	mg/dl	IL8	pg/ml
Ig G4	mg/dl	IP10	pg/ml
Ig M	mg/dl	MCP1	pg/ml
Specific Ig E Index		MIP1α	pg/ml
Cedar	Index Value	MIP1β	pg/ml
Cypress	Index Value	TNFα	pg/ml
House dust	Index Value	TNFβ	pg/ml
Dermatophagoides pteronyssinus	Index Value	VEGF	pg/ml

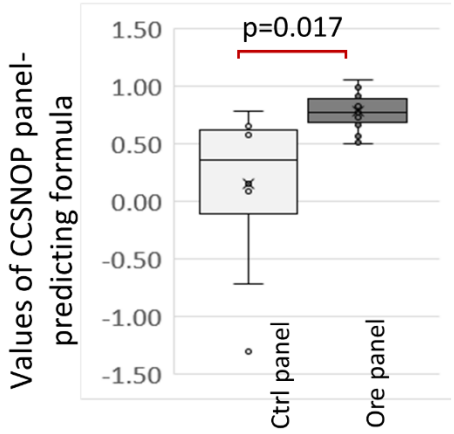
B Statistic Factors of CCSNOP panel-predicting formula

Model terms	coefficient	Significance	Importance
Constant term	0.801	0.000	
GM-CSF	-0.061	0.002	0.353
IL-12p40	-0.050	0.008	0.235
Ig G4	-0.004	0.026	0.160
Eosinophil	0.001	0.035	0.140

C

CCSNOP panel-predicting formula
=
0.801
-0.061 x GM-CSF
-0.050 x IL-12p40
-0.004 x Ig G4
+0.001 x Eosinophil counts

D



E

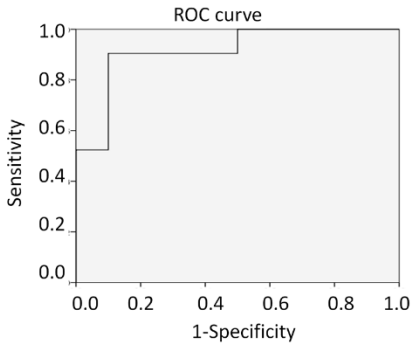


Figure 10. Formula predicting subjects exposed to CCSNOP (Ore). [A] List of parameters employed for multiple regression analysis. [B] Factors, coefficient, significance and importance of statistical factors extracted in CCSNOP panel-predicting formula. [C] The formula for CCSNOP panel prediction. [D] Using the CCSNOP panel-predicting formula, all data pertaining to GM-CSF, IL-12p40, IgG4 and eosinophil counts at sampling time 3 were substituted. Thereafter, values derived from the formula for CCSNOP (Ore) and NWC (Ctrl) subjects were plotted in the form of box-plots. A significant difference (p=0.017) was observed. [E] ROC curve of the CCSNOP panel-predicting formula, with [sensitivity] and [1-specificity] values of 0.905 and 0.100, respectively.

4. Discussion

Pollen allergies continue to be an issue for those affected in contemporary societies [1-3]. Although various strategies have been employed to deal with this medical issue, such as desensitization therapy [9-11], many patients simply endure by taking medicinals that help to relieve the symptoms until the end of the pollen dispersal season. Most of the drugs only provide symptomatic relief, and in the end, the only recourse available to many patients is to try and avoid exposure [4-6].

We investigated whether the residential environment could induce some kind of pollen allergy relief. Cosmic Garden Co., Ltd. has been selling detached houses in which powder derived from ore collected near Aso Mountain, Kumamoto Prefecture, Kyushu Island, Japan, is mixed with interior wall materials. Anecdotal evidence suggested that home occupants experienced relief of symptoms related to pollen allergy. Therefore, in our previous study, we investigated the effects of mineral-containing (CCSNOP) or control (NWC) panels on pollen allergy patients every two weeks for one hour. The severity of symptoms, changes in eosinophils, cytokines, mood (measured by POMS2), stress markers measured by sAmy, and blood samples were investigated [12]. It was found that the severity of symptoms improved with CCSNOP. Furthermore, eosinophils increased slightly but significantly in the CCSNOP group [12]. Although changes in certain cytokine levels differed between the CSNOP and NWC groups, the biological significance of this finding remains to be determined [12]. Since it seemed that CCSNOP had a demonstrably positive effect on pollen allergy patients, it was thought that an investigation comprising longer-term exposure to CCSNOP, including during the pollen dispersal season, would be instructive.

Therefore, in the present study, we decided to examine various biological indicators along with symptoms in subjects with Japanese cedar pollen allergy who were exposed to CCSNOP or NWC panels in their bedroom.

The results of this study showed that CCSNOP alleviated the symptoms of pollen allergy and that the use of medicinals decreased in the CCSNOP group. Inspection of the "pollen allergy diaries" revealed that even difficulties of daily life were reduced in the CCSNOP group, although the TMD (measured by POMS2) and the degree of stress (measured by sAmy) showed no differences between the CCSNOP and NWC groups.

However, blood sample analyses indicated that the absolute number of eosinophils tended to be lower in the CCSNOP group compared with the NWC group during the pollen dispersal season.

Cytokines, especially MCP1, IP10, CXCL10 / IP-10, CCL4 and CCL3, which are related to the onset of hay fever and the mechanism of symptom appearance are shown in Fig. 8. CCSNOP and control groups did not show significant changes. As discussed below, a formula was established to extract and detect subjects belonging to the CCSNOP group on the basis of these cytokines. These results suggest that this mineral powder panel may not have a direct effect on the pathogenesis of hay fever allergies, but may have an effect on secondary parts such as the appearance of symptoms.

Furthermore, when many cytokines were measured and a formula for detecting CCSNOP subjects was generated along with other indicators, GM-SCF and IL-12p40 were extracted along with eosinophil count and Ig G4 values. These

two cytokines are of greater importance. Additionally, when using this formula, it was revealed that blood sampling detected a significant difference in subjects exposed to CCSNOP panels for two weeks.

GM-CSF is known as a cytokine that induces differentiation of pluripotent hematopoietic stem cells into granulocyte-monocyte cells [22,23]. In relation to pollen allergy and GM-SCF, this cytokine has been reported to increase with IL-33 and IL-25 in animal models, and following the activation of neutrophils and antigen-specific T cells [24]. Additionally, one report has shown that IL-33 is activated by GM-CSF and IL-8 in the nasal mucosal epithelium of allergic rhinitis [25]. Moreover, some reports have indicated that production of GM-CSF was activated in patients with seasonal allergic rhinitis (possibly caused by pollen) [26].

Considering these reports and the prediction formula generated in this study, GM-CSF was extracted with a negative coefficient in the prediction formula, and could be utilized to detect a person staying under CCSNOP conditions. Therefore, CCSNOP may act on subjects by improving the pathophysiology of pollen allergy even at the cytokine level.

IL-12p40, along with IL-12p70, is a component of IL-12. IL-12 is well-known as a cytokine responsible for induction into Th1 cells together with IFN-γ [27,28]. Therefore, since a state with high IL-12 induces differentiation to Th1 rather than Th2, it might be that patients with pollen allergy possess reduced IL-12 production. However, IL-12p40 was also extracted with a negative coefficient in our formula. Although interpretation of this finding seems difficult, it may be that subjects exposed to CCSNOP experience decreasing levels of IL-12 over the 2-week period of stay, since they showed a reduction in the severity of symptoms during that period.

The formula generated in this study also indicated that IgG4 was extracted with a negative coefficient, even though the importance was less than that of the cytokines. Recently, IgG4 has been implicated to play a role in various diseases that have shown elevated serum IgG4, IgG4-positive plasma cell infiltration into affected tissue, and fibrosis [17-19]. However, IgG4 was initially considered in relation to the allergic condition. Production of IgG4 is induced by IL4 and IL-13, which are Th2-type cytokines mainly involved in allergic reactions under antigen stimulation. Thus, the negative coefficient of IgG4 in the generated formula may indicate a reduction in allergic reactions in subjects exposed to CCSNOP conditions.

In our previous observational study, we were able to confirm that the symptoms of hay fever improved in the 1-hour CCSNOP environment, but that was a unique environment of only 1 hour. While the subjects were living in a normal period, the effect was observed by setting up a CCSNOP environment in the bedroom at home, and as a result, symptoms were alleviated and medication

was avoided. In addition, although there was no direct effect on individual cytokines allegedly associated with allergies, as indicated, there was some It is almost certain that it has an effect and that it alleviates allergic symptoms, and the mechanism is almost unknown at present, probably due to the decrease in pollen itself in the air. Will of that. The change of the immune system that are represented in the current official, direct or effect of the of CCSNOP, or, or relaxation resulted in a change of the of such symptoms, at present is unknown.

There were no adverse effects in any of the subjects exposed to CCSNOP conditions in this study. Additionally, Cosmic Garden Co. Ltd. has sold more than 200 homes with powder or with this specific ore and no adverse effects have been reported.

Originally, it would be best if the effects of CCSNOP could be verified using animal models. However, it is very difficult to create a situation where the animal model is exposed to the environment by CCSNOP or NWC while building and using an animal model of hay fever in our laboratory. In future, it will be necessary to observe such a situation through some joint research. However, occupants of CCSNOP-containing detached homes sold by Cosmic Garden Co., Ltd. have already provided anecdotal reports of hay fever symptom relief. Consequently, an impact following the use of this specific ore could be expected.

The limitation of this study was that it comprised a small number of subjects and all results were extracted by comparing the CCSNOP group with the NWC group. The changes over time in this group did not yield a very definitive finding. However, we believe that exposure to CCSNOP reduced allergy-related symptoms in addition to affecting certain biological reactions in pollen allergy patients. Long-term monitoring of individuals living in homes containing this ore powder as part of the inner wall material may yield more information regarding the effects of CCSNOP on patients with pollen allergies.

5. Conclusions

Our investigations showed that use of CCSNOP resulted in relief of symptoms and reduced use of therapeutics. Moreover, the ratio of eosinophil count decrease during exposure was higher in the CCSNOP group. Furthermore, a formula for measuring various cytokines and other parameters was established and clearly showed a distinction between the CCSNOP and NWC groups. In this formula, GM-SCF, IL-12p40, IgG4 and eosinophil count were extracted. These results indicated that CCNSNOP has a beneficial effect on pollen allergy patients. Future studies shall engage in long-term monitoring of pollen allergy patients who will utilize this mineral powder for at least one year.

Author Contributions: Conceptualization, Youichi Murakami; Data curation, Suni Lee, Shoko Yamamoto, Maiko Hamana, Hiroshi Okamoto and Tamayo Hatayama; Funding acquisition, Yoshio Fujii and Youichi Murakami; Investigation, Suni Lee, Shoko Yamamoto, Maiko Hamana, Hiroshi Okamoto, Tamayo Hatayama and Takemi Otsuki; Methodology, Suni Lee, Shoko Yamamoto, Maiko Hamana, Hiroshi Okamoto, Tamayo Hatayama and Takemi Otsuki; Project administration, Fukusou Danbara, Youichi Murakami and Takemi Otsuki; Supervision, Yoshio Fujii, Youichi Murakami and Takemi Otsuki; Writing – original draft, Suni Lee; Writing – review & editing, Maiko Hamana, Hiroshi Okamoto and Takemi Otsuki.

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Conflicts of Interest: The Wadakohsan Corp. provided funding for this study and authors M.H, F.D. and Y.M. belong to this corporation. The Cosmic Garden Co. Ltd. provided CCSNOP and NWC panels for this study, author H.O. belongs to this company, and author Y.F. is President of this company. The department of Hygiene, Kawasaki Medical School, where all other authors belong, received aforementioned funding and performed the research work. Furthermore, no issues were found from an ethical viewpoint after the monitoring and audit were completed.

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