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ASSOCIATION BETWEEN ENVIRONMENTAL CHANGES AND PHARMACY VISITS IN PATIENTS WITH RELATIVELY FAVORABLY CONTROLLED ASTHMA

Kentaro Iwade*, Shizuka Shimoji, Hidenori Masaki, Kouichi Tanabe, Nobuyuki Goto and Fumiko Ootsu

Meijo University, Drug Informatics 150 Yagotoyama, Tenpaku-ku, Nagoya, Aichi 468-0077.

***Corresponding Author: Kentaro Iwade**

Meijo University, Drug Informatics 150 Yagotoyama, Tenpaku-ku, Nagoya, Aichi 468-0077.

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INTRODUCTION

When the seasons change, pharmacists at insurance pharmacies often instruct patients who are prescribed anti-asthmatic drugs (asthma patients) to "please watch out for the onset of asthmatic attacks as the seasons change". Pharmacists at insurance pharmacies anecdotally acknowledge that the number of asthma patients increases when the temperature declines. There are several reports about the associations between climate / environmental changes and the appearance of asthma symptoms, and Kobayashi, et al and Ishizaki, et al reported that asthma symptoms are likely to appear when the temperature differences on the previous day are over minus 3 degrees Celsius (-3°C).[1,2] Piccoclo, et al also reported that the number of emergency outpatient visits by asthma patients increased when relative humidity became low.[3] However, most of these reports regard severe asthma symptoms, emergency outpatient visits, hospitalizations, and symptoms taking a sudden turn. Asthma patients who simply visit insurance pharmacies have comparatively favorable asthma control on a daily basis, and it is considered that a rapid worsening of their symptoms due to climate / environment changes is less likely to happen. However, it is suggested that even mild asthma attacks and having a cough could lessen their QOL. There have been few reports about how climate / environment changes affected such patients from an epidemiological perspective over a long period of time. Japan's "Declaration on the Creation of the World's Most Advanced IT Nation" on June 14th, 2013 declared that existing industries, business and regions will be revitalized by utilizing enormous amounts of data, so-called 'big data' owned by public and private entities.[4] With the spread of electronic patient drug profiles and electronic receipts, insurance pharmacies now have big data collections which are significant, useful, and enormous, and which can be utilized easily. Several reports which studied flu infection status by analyzing data on the amount of prescription drugs taken used big data from insurance pharmacies.[5-7] This purpose of this study is to elucidate how climate and environmental changes affect the QOL of asthma patients who have relatively favorable asthma control, and we investigated the associations between the fluctuation in the number of asthmatic patients who visited insurance pharmacies and climate / environmental changes.

METHODS

1) Method for identifying the number of visiting patients

The number of asthma patients who visited insurance pharmacies is set as an index of deterioration in QOL in this study. We selected patients who were prescribed anti-asthmatic drugs (asthma patients); who live in Osaka; who visited two chain insurance pharmacies in Osaka, Japan, which are affiliated with the Saera pharmacy group, and we identified the age, sex and number of visiting patients per day between Jan 1st, 2011 and March 31st, 2015. We used data stored in the insurance pharmacies' receipt computers and investigated the data without identifying individuals. Anti-asthma drugs are defined as bronchodilator agents, xanthine derivatives, isoprenaline derivatives, chlorprenaline preparations, salbutamol preparations, other bronchodilator agents, other agents affecting respiratory organs, and other anti-allergic agents. We excluded drugs for chronic obstructive pulmonary disease and tulobuterol adhesive skin patches which are categorized into other bronchodilator agents. We also excluded anti-allergenic drugs which are not approved for bronchial asthma in the category of other anti-allergic agents. The prescribed adult and pediatric average dosages of inhaled steroids (μg/person) were measured separately in order to understand the asthma severity level of the target patients. We converted the dosages of steroids to the dosage of fluticasone propionate (FP) according the guidelines in "Asthma Prevention and Management Guideline 2018". As a target for comparison, we identified the age, sex, and number of visiting patients per day who had been prescribed antihyperlipidemic drugs (patients with hyperlipidemia). The associations between climate / environmental changes and diseases requiring antihyperlipidemic drugs have also not been elucidated. Antihyperlipidemic drugs are defined as agents for hyperlipidemias, linoleic acid preparations, lecithin reparations, clofibrate derivatives preparations and other agents for hyperlipidemias. We excluded days when a pharmacy was closed all day, closed before noon, and non-consultation days of medical institutions near pharmacies that have a department of respiratory disease (Fig. 1).

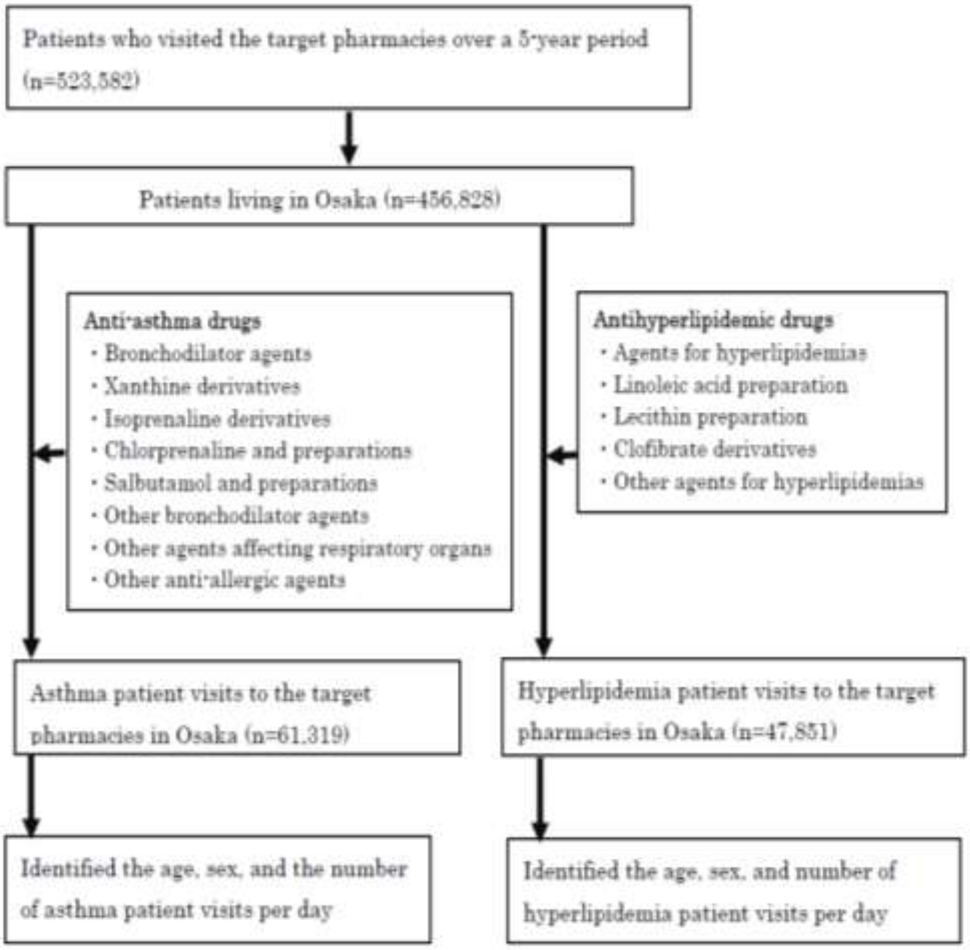


Fig. 1: Methods for identifying the number of asthma patient visits and the number of hyperlipidemia patient visits to the target pharmacies.

2) Climate and environmental data

We investigated the average temperature (temperature), average relative humidity (humidity), and average barometric pressure observed by the Osaka District Meteorological Agency (at 34°40.9'N; 135°31.1'E) between Jan 1st, 2011 and March 31st, 2015. This information was made publicly available by the Japan Meteorological Agency (http://www.jma.go.jp/jma /index.html). We also used PM2.5 concentration data that was captured using the β-ray absorption method by Kokusetsu-Osaka (1-3-62 Nakamichi, Higashinari-ku, Osaka City) between Jan 1st, 2011 and March 31st, 2013 from an environmental numerical database which has been made publicly available by the National Institute for Environmental Studies (http://www.nies.go.jp/ index.html). Regarding temperature, Kobayashi, et al and Ishizaki, et al reported that asthma attacks are likely to appear on a day when the temperature has decreased 3 degrees Celsius (-3°C) compared with the previous day.[1,2] Thus, we defined a day when the temperature had decreased over 3°C compared with the previous day as a ‘change day’. Concerning humidity, Kurosaka, et al and Yamanaka, et al reported that negative correlations were observed between humidity and asthma attacks and respiratory diseases.[8,9] Thus, we defined a day when humidity decreased over -10% compared with the previous day as a change day, based on the numerical criteria studied by Mireku, et al.,[10] Concerning barometric pressure, there are several reports about the onset of asthma attacks when barometric pressure either increases.[2,9] or decreases.[3,11] Thus, we defined a day when the barometric pressure was 5 hPa higher than the previous day as a change day (increased) and a day when the barometric pressure was 5 hPa lower than the previous day as a change day (decreased), based on the numerical criteria suggested by Sugimura, et al.[12] Regarding PM2.5 concentration, Kloog, et al and Zanobetti, et al reported that the number of patients with respiratory diseases making emergency outpatient visits and being hospitalized increased on days when PM2.5 concentration was 10μg/m^{3}higher compared with the previous day.[13,14] Thus, we defined days when PM2.5

concentration was 10µg/mhigher as a change day (Table 1).

Table 1. Criteria of temperature, humidity, barometric pressure, and PM2.5 concentration in the change day groups and non-change day groups.

Climate and environmental factors	The change day group	Non-change day group
mean temperatures	decreasion of over -3℃	change range of ±0.3℃
the relative humidity	decreasion of over -10%	change range of ±1.0%
the barometric pressure	rise of over 5 hPa/decrease of over 5 hPa	change range of ±0.5hPa
the PM2.5 concentration	increase of over 10µg/㎥	change range of ±1.0µg/㎥

We defined days when the temperature, humidity, barometric pressure and PM2.5 changed only within ±10% based on the previous criteria set for climate and environmental factors in this study for change days as non-change days because there are no previous reports from which to source the criteria for non-change days. We show our method for determining change and non-change days regarding temperature in a diagram in Fig. 2. Because -3°C is a temperature standard, we defined days when the temperature changes within ±10%, specifically only ±0.3°C, as non-change days.

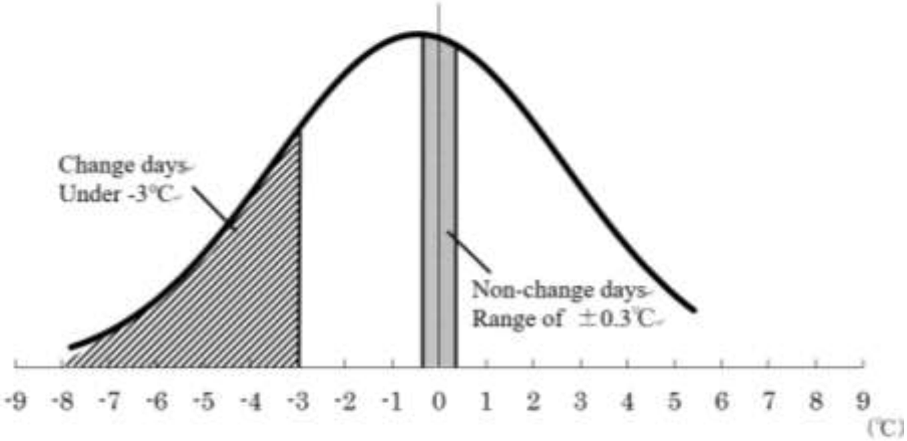


Fig. 2: Methods of determining mean temperatures for change days and non-change days.

3) Method of analysis

We associated the number of asthma patient visits per day with the data of temperature, humidity, barometric pressure, and PM2.5 concentration on that day. We divided the number of asthma patients into 2 groups: change day group (the number of asthma patients who visited the target pharmacies the day after a change day); non-change day group (the number of asthma patients who visited the target pharmacies the day after a non-change day), and compared the average number of asthma patients in each group. We also compared the average number of patients with hyperlipidemia between two groups. We analyzed the mean numbers of the respective patients in their groups using Student's t-test and used SPSS Statistics 24 (IBM®) to perform statistical analysis. This study has been approved by the Ethical Review Board, Faculty of Pharmacy, Meijo University (H28-3).

RESULTS

523,528 total patients visited the target pharmacies over the 5-year period we examined, and 456,828 of those patients live in Osaka. 61,319 asthma patients and 47,861 patients with hyperlipidemia living in Osaka visited the target pharmacies during the 5-year period. The subjects are patients with asthma controlled by low to medium dosages of FP (adult dose: 202.1±103.5㎍/person/day; pediatric dose: 89.1±66.1㎍/person/day). There were 125 temperature change days and 286 non-change days. There were 385 humidity change days, and 276 non-change days. There were 256 change days when the barometric pressure increased, 385 change days when it decreased, and 270 non-change days. There were 134 PM2.5 concentration change days, and 246 non-change days.

1) Association between temperature and the number of asthma and hyperlipidemia patient pharmacy visits

The mean number of asthma patients in the temperature change day group was 25.4±8.5 and 23.7±8.3 in the non-change day group (Fig. 3). Thus, the number of patients in change day group was significantly larger compared with the non-change day group. The mean number of patients with hyperlipidemia in the change day group was 19.2±7.1, and it was 18.8±7.6 the non-change day group. Thus, there was no significant difference between the change day group and non-change day group.

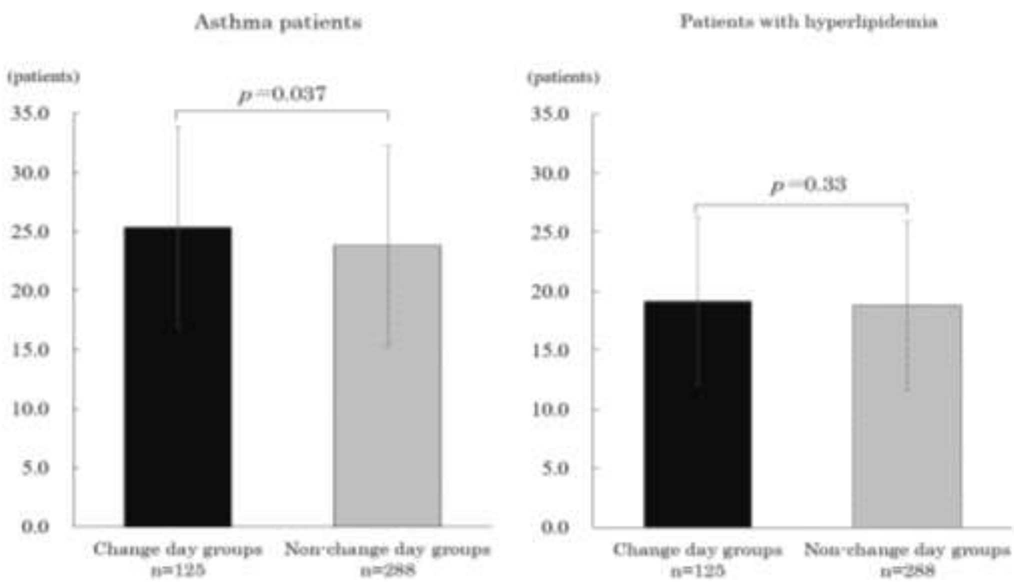


Fig. 3: Mean number of patients in the temperature change day groups and non-change groups.

2) Association between humidity and the number of asthma and hyperlipidemia patient pharmacy visits

The mean number of asthma patients in the humidity change day group was 24.9±8.3, and it was 23.6±7.7 in the non-change day group (Fig. 4). The mean number of patients with hyperlipidemia in the humidity change day group was 19.8±7.6 and it was 18.9±7.2 in the non-change day group. There was no significant difference between the change and non-change day groups.

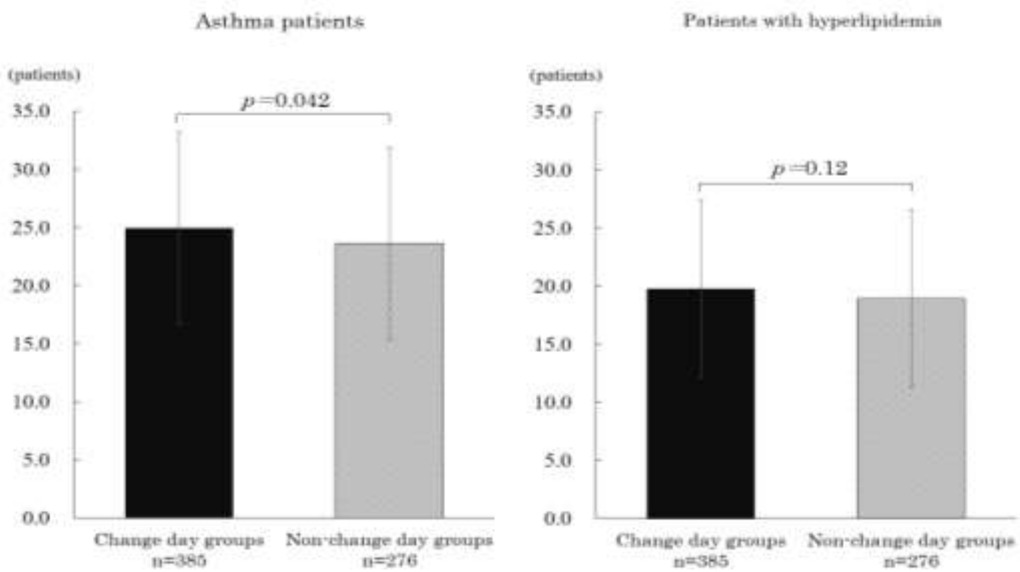
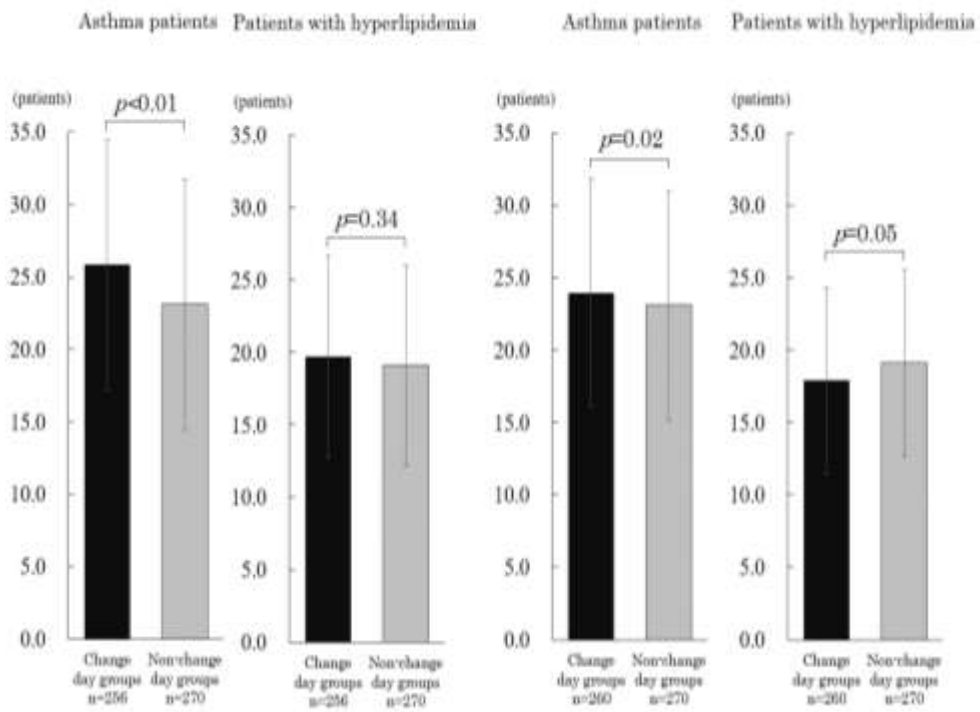


Fig. 4: Mean number of patients in the relative humidity change day groups and non-change day groups.

3) Association between barometric pressure and the number of asthma and hyperlipidemia patient pharmacy visits

The mean number of asthma patients in the change day group when barometric pressure increased was 25.8±8.6, and it was 23.1±7.5 in the non-change day group (Fig. 5). Thus, the number of asthma patients in the change day group when barometric pressure increased was significantly larger compared with the non-change day group. On the other hand, the mean number in the change day group when barometric pressure decreased was 23.9±7.8, and there was no significant difference between the change day group and non-change day group. The mean number of patients with hyperlipidemia in the change day group when barometric pressure increased was 19.7±6.9, and it was 19.1±7.6 in the non-change day group. Thus, there was no significant difference between the two groups. The mean number in the change day group when barometric pressure decreased was 17.9±6.4; thus, there was no significant difference between the decreased barometric pressure change day and non-change day groups.



Change day groups (relative humidity increased) Change day groups (relative humidity decreased)

Fig. 5: Mean number of patients in the barometric pressure change day groups and non-change day groups.

4) Association between PM2.5 concentration and the number of asthma and hyperlipidemia patient pharmacy visits.

The mean number of asthma patients in the PM2.5 concentration change day group was 26.6±8.5, and it was 23.8±8.2 in the non-change group (Fig. 6). Thus, the number of asthma patients in change day group was significantly larger compared with the non-change day group. The mean number of patients with hyperlipidemia in the change day group was 18.1±7.2, and it was 18.1±7.3 in the non-change day group. Thus, there was no significant difference between the two groups.

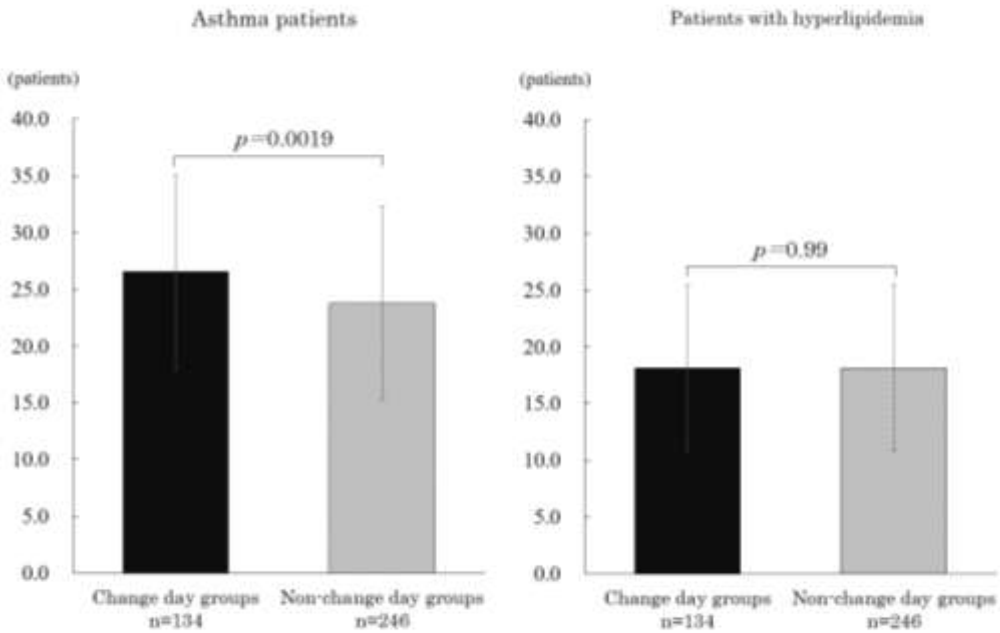


Fig. 6: Mean number of patients in the PM2.5 concentration change day groups and non-change day groups.

DISCUSSION

There have been many reports that climate changes could relieve or aggravate different disease symptoms up until the present. Patients also note anecdotally that climate changes affect their physical condition. “A survey on association between health and climate” conducted by the Terumo Corporation showed that 81% of people believed that there is an association between “climate and seasonal changes" and 'health condition"; 73% of people reported that they had experienced the influence of "climate and seasonal changes" on their health condition(s). The number of asthma patients who visited pharmacies on a day when the temperature was at least -3℃ lower compared with the previous day was significantly larger than days when the temperature did not drop at least -3℃ the previous day. Our study suggests that asthma patients who have relatively favorable asthma control might experience worsened asthma symptoms when the temperature decreases because patients with hyperlipidemia showed no symptom changes in this study when the temperature decreased. Breathing resistance is significantly increased by inhaling cold air,[16] and it was reported that bronchospasms are caused by directly inhaling cold air orally.[16,17] Therefore, the asthma patients' symptoms might have been worsened by inhaling cold air when the temperature was -3℃ lower than the previous day. On the other hand, Wells, et al reported that inhaling cold air increased breathing resistance, while the body simply being exposed to cold air did not affect it.[18] Therefore, it is thought that avoiding inhaling cold air might prevent asthma symptoms from worsening. Wearing a mask to avoid directly inhaling outside air could be effective to prevent asthma symptoms from worsening when the temperature is -3℃ lower than the previous day. Kurosaka, et al reported that asthma symptoms worsen when relative humidity decreases,[8] and Nakayama, et al reported the negative association between respiratory dysfunction and relative humidity.[9] Our study showed that the number of asthma patients visiting the target pharmacies significantly increased when relative humidity decreased over -10% compared with the previous day. This suggests the possibility that asthma symptoms might worsen when humidity decreases since patients with hyperlipidemia did not increase their pharmacy visits under the same conditions. It is reported that airway contraction was observed when pulmonary resistance was increased by the hyperventilation of dry air in animal tests.[19,20] As with cold air, it is thought that avoiding direct inhalation of dry air helps prevent the worsening of asthma symptoms. Additionally, using humidifiers in the house could be effective in preventing dry air. In the winter, the air outside becomes dry and the temperature drops. It could be also effective in this case also for asthma sufferers to wear masks outside to prevent the direct inhalation of dry and cold air. Ishizaki, et al and Kurosaka, et al reported that asthma attacks increased when barometric pressure increased.[2,8] On the other hand, Piccolo, et al and Miyamoto, et al reported that asthma attacks also increased when barometric pressure decreased.[3,11] The reports are varied in terms of high and low barometric pressure. Our study showed that the number of asthma patients visiting the target pharmacies increased when barometric pressure increased, and that there was no change in the number of patients with hyperlipidemia visiting when barometric pressure either increased or decreased. Thus, we could observe a possible association between barometric pressure increase and the number of asthma patients visiting the target pharmacies. The weather is favorable when the barometric pressure increases in our experience; thus, it is considered that the possibility of asthma symptoms worsening is low. Nakano, et al performed a study using an artificial weather room and reported that lung ventilation performance was low when barometric pressure decreased, and that this low performance is one of the factors that contributes to the onset of an asthma attack.[21] Winter is a season when temperature and humidity dramatically change (cold and dry), and asthma patients in winter are often affected by decreases in temperature and humidity on a daily basis. Decreases in temperature and humidity at certain levels in winter worsen asthma symptoms, and are likely to have caused asthma patients to visit the insurance pharmacies next day. On the other hand, barometric pressure suddenly changes as a typhoon passes, it takes time until worsening asthma symptoms associated with decrease in pressure. Goldstein noted that the number of asthma patients with the onset of asthma symptoms increased 1-3 days after a cold front passed; thus, there might be a gap between the day they visit insurance pharmacies and the day of barometric pressure change.[22] Therefore, because the visiting number of asthma patients increased when barometric pressure decreased and then increased next, it can be considered that the visiting number of asthma patients was increased compared with the previous day as this study showed in the results. It is difficult to avoid barometric pressure changes, but it could be effective to instruct asthma patients to take care to be especially compliant in taking anti-asthmatic drugs and to provide information about their usage when a decrease in barometric pressure can be predicted with the approach of an atmospheric depression or typhoon. PM2.5 are small particles less than 2.5μm which originate from various sources including artificial fuels, such as chemical fuel and biomass fuel. The mechanism of PM2.5 worsening bronchial asthma symptoms reported in animal tests is that different particle substances in PM2.5 evoke an inflammatory response in the respiratory tract and lungs and work as adjuvants which provoke an antigen-antibody reaction in the respiratory tract.[23] PM2.5 particles are small, and they can reach the bronchioles and alveoli and cause inflammation. Therefore, wearing masks in order to avoid direct inhalation of PM2.5 is a preventative measure. It has been reported that the number of patients with respiratory disease who made emergency outpatient visits and were hospitalized increased when PM2.5 concentration increased over 10μg/㎥ compared with the previous day,[13,14] and this study also showed that the number of asthma patients visiting the target pharmacies significantly increased when PM2.5 concentration increased over 10μg/㎥ compared with the previous day. Thus, our study showed the possibility of worsened asthma symptoms associated with an increase in PM2.5 concentration since there was no change in the symptoms of patients with hyperlipidemia. Therefore, remaining indoors when

PM2.5 concentration increases over 10μg/㎥ compared with the previous day and wearing masks outside could help to prevent the onset of an asthma attack. The subjects in this study were patients with mild to moderate asthma patients [based on their inhaled FP dosage] who visited insurance pharmacies. However, our study suggests the possibility that climate and environmental changes could worsen asthma symptoms and lessen QOL of not only the uncontrolled and severe asthma patients, but also of asthma patients who have relatively favorable asthma control and visit insurance pharmacies. Thus, it is possible that pharmacists at insurance pharmacies who offer predictive and preventative types of instruction on the use of medication and health guidance to each asthma patient based on the weather forecast and PM2.5 concentration data could be effective in preventing worsened asthma symptoms. In fact, according to the results of the previously mentioned survey "Association between health and climate" conducted by the Terumo Corporation, 78% of those surveyed answered that being provided information on the association between climate and health conditions would be useful, and 92% of those who often experienced the climate's influence on their health condition answered that it would be especially useful.[15]

CONCLUSIONS

This study investigated 2 chain pharmacy stores in Osaka affiliated with the Saera pharmacy group where the number of asthma patient visits is especially high. Our study of the association between changes in climate and environmental factors and a decrease or increase in asthma symptoms could be useful for the asthma patients in Osaka, but its application is uncertain for other areas. The characteristics of climate and environmental change differ throughout the world; thus, it might be necessary to conduct similar investigations elsewhere. There are many reports that suggest that changes in climate and environment increased or decreased symptoms of other diseases; therefore, it is necessary to investigate the possibility that new evidence for other diseases can be discovered by using big data from insurance pharmacies. However, we believe in the value of developing a method to confirm the influence of climate and environmental changes on patient outcome by using big data from insurance pharmacies and open climate and environmental data. We also believe that this method could potentially be applied to other diseases that are also influenced by climate and environmental changes. We would like to continue investigating to show that such evidence could be useful to prevent asthma symptoms from worsening by prospectively investigating associations between changes in climate and environment and asthma symptom changes.

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