Similar distribution of peripheral blood eosinophil counts in European and East Asian populations from investigations of large-scale general population studies: the Nagahama Study

To the Editor:

We read with interest the study by Hartl *et al.* [1] entitled "Blood eosinophil count in the general population: typical values and potential confounders", recently published in the *European Respirator Journal*. This is an excellent paper showing the distribution of blood eosinophil counts in the general population, including more than 10 000 participants. The authors found a right-skewed, non-normal distribution with the tail towards the higher counts.

Before the 2000s, various techniques to evaluate airway inflammation using induced sputum or other direct sampling from airways had been developed, but for daily clinical practice, progress in this field was quite slow. Alternatively, the potential usefulness of peripheral blood eosinophil count was suggested almost half a century ago [2]. Then, in recent developments in clinical research, total peripheral eosinophil counts have been revealed as useful biomarkers to diagnose several diseases and especially to predict the response for specific treatments in respiratory diseases, such as asthma and COPD [3–5]. This biomarker has returned to the limelight and has become a trending research topic, in particular for the management of respiratory diseases [6]. However, there are still some difficulties for some to digest and questions on the validity, accuracy, and diagnostic value of the blood eosinophil count. Hartl *et al.* [1] described these issues.

Consequently, as they referred our recent paper from the Nagahama Prospective Genome Cohort for Comprehensive Human Bioscience (The Nagahama Study), which is currently an ongoing community-based prospective observational cohort study in the Japanese general population, we have great interest in confirming their results in our study population. We have approximately 10 000 participants, and we evaluated 9789 participants in our recent reports [7]. The mean±SD age was 53.6±13.4 years, and two-thirds (66%) were female. The inclusion criteria were age 30 to 74 years and without current serious diseases or physical impairment. Regarding these points, our study population had slightly different parameters than that of Hartl *et al.* [1]. However, as shown in figure 1, the distribution of peripheral blood eosinophil counts seems quite similar to that found by Hartl *et al.* [1], ranging from 0 to 2139 cells·μL^{-1}, and the counts were non-normally distributed. The geometric mean value was 155.3 cells·μL^{-1}, and the median value was 120.0 cells·μL^{-1}.

In a comparison of both studies, the median value (120.0 and 130 cells·μL^{-1}) and 75th percentile value (200.2 and 210 cells·μL^{-1}) were quite similar, and asthmatic subjects were approximately 4% in both populations. Although our study population had a smaller body mass index (BMI) (22.3 *versus* 24.8 kg·m^{-2}), elderly participants without children (53.6 *versus* 44.9 years), and fewer smoking habits (never/former/current; 65/20/15% *versus* 49.7/28.6/21.7%), it is interesting that our distribution looked quite similar. Moreover, we examined changes in blood eosinophil counts at the 5-year follow-up period.

Cite this article as: Sunadome H, Sato S, Matsumoto H, *et al.* Similar distribution of peripheral blood eosinophil counts in European and East Asian populations from investigations of large-scale general population studies: the Nagahama Study. *Eur Respir J* 2021; 57: 2004101 [https://doi.org/10.1183/13993003.04101-2020].

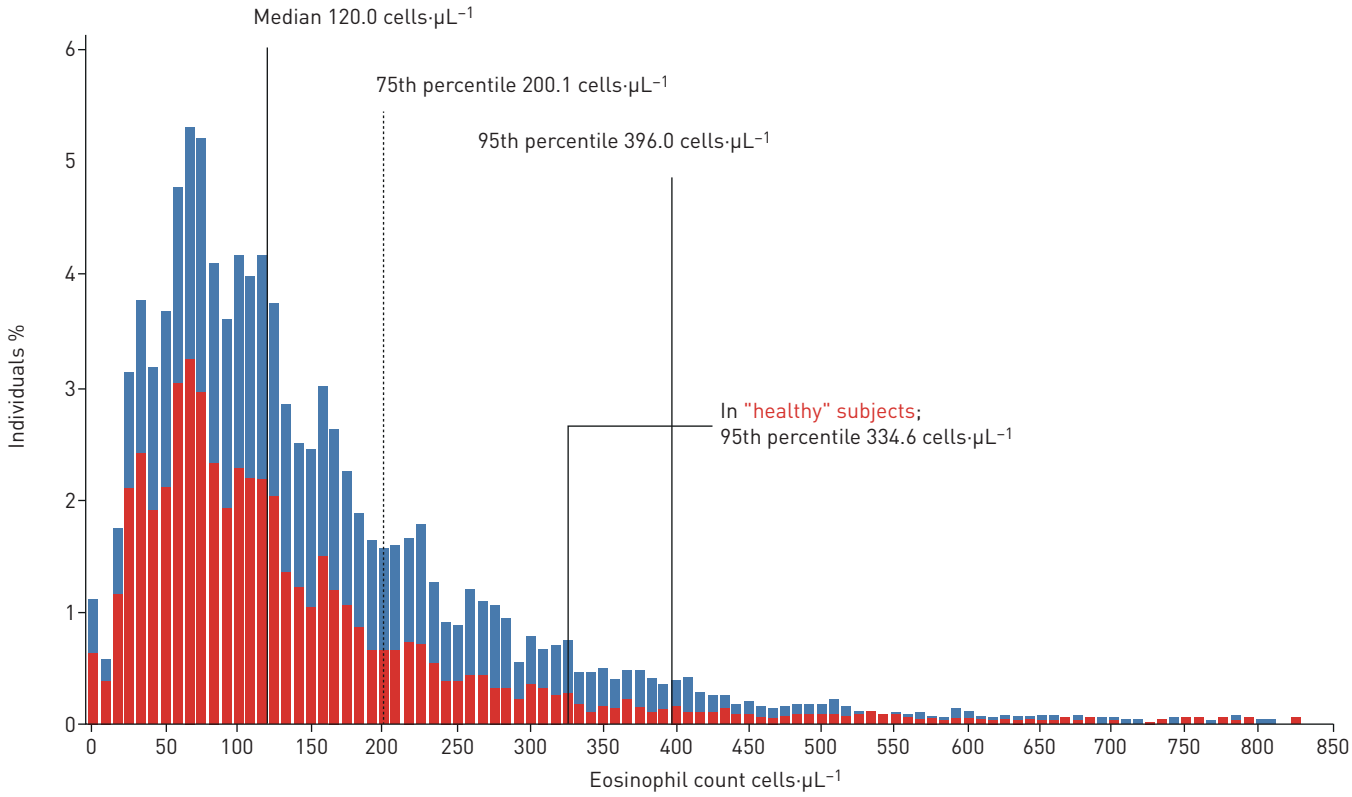

FIGURE 1 Frequency distribution of blood eosinophil counts in the Nagahama study. Red bars indicates distributions in "healthy subjects", who were not current smokers, were not obese (*i.e.* body mass index was <30 kg·m^{-2}), had not been diagnosed with asthma nor allergic rhinitis, and had no airflow limitation (ratio of forced expiratory volume in 1 s to forced vital capacity ⩾0.7).

Among the 8287 participants who underwent follow-up examination [7], the mean change from baseline was −10.7±121.9 cells·μL^{-1}, the median ratio (range) of change was −7.8% (−35.7 to 29.5%), and the geometric mean, median, 25th and 75th percentiles were 143.1, 110.0, 68.8 and 182.9 cells·μL^{-1}, respectively. Interestingly, the distribution in the follow-up study was quite similar to that at the baseline evaluation, as it was in the Hartl *et al.* [1] study. Since we demonstrated a nonlinear relationship between BMI and blood eosinophil count, variation within populations should be more complicated. Although other confounders for eosinophil count might have affected such fluctuation or stabilising phenomena of distribution of eosinophil count, from this comparison and observation, it can be considered that the distribution of eosinophils in the general population-based data may be reproducible, and can be extrapolated to the distribution in other populations.

Moreover, as in the study reported by Hartl *et al.* [1], we also evaluated the subjects who were considered "healthy" in our population, excluding individuals who were current smokers, were obese (BMI ⩾30 kg·m^{-2}), had been diagnosed with asthma or allergic rhinitis, and had airflow limitation (ratio of forced expiratory volume in 1 s to forced vital capacity <0.7). In total, 4921 "healthy" subjects were included (1309 males and 3612 females), and the 5th to 95th percentiles of eosinophil counts were 29.6–392.1 cells·μL^{-1} in males and 28.1–308.0 cells·μL^{-1}, which is quite similar to the results reported by Hartl *et al.* [1] (30–330 cells·μL^{-1} in males and 30–310 cells·μL^{-1} in females), at least in females. Vedel-Krogh [8] indicated in the accompanying editorial that the healthy upper limit of peripheral eosinophil counts could be 300 cells·μL^{-1}, which is almost the same as the cut-off values to predict potential benefits of inhaled corticosteroids for COPD patients [5, 6]. Although they usually constitute less than 5% of all leukocytes [9], eosinophil counts have been found to range from 50 to 500 cells·μL^{-1} in recent reports [10]; for example, "300" cells·μL^{-1} could be meaningful in clinical settings, even in different populations.

To conclude, peripheral blood eosinophil count is quite easy to assess and has various possible powers to diagnose, and the upper limit of normal distribution of eosinophils could be useful to find remarkable subjects. It is important to recognise the normal distribution of peripheral blood eosinophils with regard to variation and reproducibility in each subject.

Hironobu Sunadome[1], Susumu Sato[2], Hisako Matsumoto[2], Kimihiko Murase[1], Takahisa Kawaguchi[3], Yasuharu Tabara[3], Kazuo Chin[1], Fumihiko Matsuda[3] and Toyohiro Hirai[2]
[1]Dept of Respiratory Care and Sleep Control Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan. [2]Dept of Respiratory Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan. [3]Center for Genomic Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan.

Correspondence: Susumu Sato, Dept of Respiratory Medicine, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan. E-mail: ssato@kuhp.kyoto-u.ac.jp

Received: 8 Nov 2020 | Accepted: 9 Nov 2020

Acknowledgements: The Nagahama study conforms to the standards of the Declaration of Helsinki. The Ethics Committee of the Kyoto University and the Nagahama Municipal Review Board approved this study protocol (Registry ID G0278). We obtained written informed consent from all the participants. We are grateful to Nagahama City Office and the nonprofit organisation Zeroji Club for their assistance in performing the Nagahama study. We are grateful to Yoshiro Toyama, Masanori Azuma, Ryo Tachikawa and Morito Inouchi (Kyoto University Graduate School of Medicine, Kyoto, Japan) for their assistance in collecting data.

Conflict of interest: H. Sunadome reports grants from Philips-Respironics, Teijin Pharma, Fukuda Denshi, Fukuda Lifetec Keiji and ResMed, outside the submitted work. S. Sato reports grants from Nippon Boehringer Ingelheim, outside the submitted work. H. Matsumoto has nothing to disclose. K. Murase reports grants from Philips-Respironics, Teijin Pharma Fukuda Denshi, Fukuda Lifetec Keiji and ResMed, outside the submitted work. T. Kawaguchi has nothing to disclose. Y. Tabara reports grants from The Japan Agency for Medical Research and Development (AMED) and The Ministry of Education, Culture, Sports, Science and Technology in Japan, during the conduct of the study. K. Chin reports grants from the Japanese Ministry of Education, Culture, Sports, Science and Technology, grants from the Intractable Respiratory Diseases and Pulmonary Hypertension Research Group, the Ministry of Health, Labour and Welfare, Japan, grants from the Center of Innovation Program, and the Global University Project from Japan Science and Technology Agency, Japan Agency for Medical Research and Development, grants from the Research Foundation for Healthy Aging, grants from the Health, Labour and Welfare Sciences Research Grants, Research on Region Medical, during the conduct of the study; grants from Philips-Respironics, Teijin Pharma, Fukuda Denshi, Fukuda Lifetec Keiji and ResMed, outside the submitted work. F. Matsuda reports grants from The Japan Agency for Medical Research and Development (AMED), The Ministry of Education, Culture, Sports, Science and Technology in Japan and Takeda Medical Research Foundation, during the conduct of the study. T. Hirai has nothing to disclose.

Support statement: This study was funded by a University Grant, a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology in Japan (25293141, 26670313, 26293198, 17H04182, 17H04126, 17H04123, 18K18450), the Center of Innovation Program, and the Global University Project from Japan Science and Technology Agency, Japan Agency for Medical Research and Development (AMED) under grant numbers dk0207006, dk0207027, ek0109070, ek0109283, ek0109196, ek0109348, kk0205008, ek0210066, ek0210096, ek0210116, and le0110005, grants from the Japanese Ministry of Education, Culture, Sports, Science and Technology, the Intractable Respiratory Diseases and Pulmonary Hypertension Research Group from the Ministry of Health, Labour and Welfare of Japan (H29-intractable diseases-general-027), the Takeda Medical Research Foundation, Mitsubishi Foundation, Daiwa Securities Health Foundation, Sumitomo Foundation, the Research Foundation for Healthy Aging, and Health, Labour and Welfare Sciences Research Grants, Research on Region Medical (H28-iryo-ippan-016, H30-iryo-ippan-009). The Dept of Respiratory Care and Sleep Control Medicine is funded by Philips-Respironics, Fukuda Denshi, Fukuda Lifetec Keiji, and ResMed to Kyoto University. Funding information for this article has been deposited with the Crossref Funder Registry.

References

1 Hartl S, Breyer M-K, Burghuber OC, *et al.* Blood eosinophil count in the general population: typical values and potential confounders. *Eur Respir J* 2020; 55: 1901874.
2 Horn BR, Robin ED, Theodore J, *et al.* Total eosinophil counts in the management of bronchial asthma. *N Engl J Med* 1975; 292: 1152–1155.
3 Brightling C, Greening N. Airway inflammation in COPD: progress to precision medicine. *Eur Respir J* 2019; 54: 1900651.
4 Pavord ID, Korn S, Howarth P, *et al.* Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012; 380: 651–659.
5 Pavord ID, Agusti A. Blood eosinophil count: a biomarker of an important treatable trait in patients with airway disease. *Eur Respir J* 2016; 47: 1299–1303.
6 Singh D, Agusti A, Anzueto A, *et al.* Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease: the GOLD science committee report 2019. *Eur Respir J* 2019; 53: 1900164.
7 Sunadome H, Matsumoto H, Izuhara Y, *et al.* Correlation between eosinophil count, its genetic background and body mass index: The Nagahama Study. *Allergol Int* 2020; 69: 46–52.
8 Vedel-Krogh S. The search for the "healthy" blood eosinophil count. *Eur Respir J* 2020; 55: 2000473.
9 Brigden M, Graydon C. Eosinophilia detected by automated blood cell counting in ambulatory North American outpatients. Incidence and clinical significance. *Arch Pathol Lab Med* 1997; 121: 963–967.
10 Valent P, Klion AD, Horny H-P, *et al.* Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. *J Allergy Clin Immunol* 2012; 130: 607–612.