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ORIGINAL ARTICLE

Blood hemoglobin levels of the general population residing at low range altitudes

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ABSTRACT

BACKGROUND

Polycythemia often develops in the highland areas. However, it remains to be clarified whether blood hemoglobin levels in the general population are affected by elevations above sea level of <1,000 m.

METHODS

This ecological study targeting secondary medical areas in Japan considered residential altitude at 0–800 m as the exposure and the mean hemoglobin level of the inhabitants aged between 40–44 years as the main outcome, based on the data extracted from the nationwide Special Health Checkup for 2021. The secondary outcome was the proportion of examinees with low hemoglobin levels. The results were validated using a 2018 dataset.

RESULTS

Individual data from approximately 1.21 million women and 1.93 million men in 335 secondary medical areas were summarized. When these areas were categorized into four groups by their altitude, the mean hemoglobin level at 600–800 m was elevated with a mean difference of 0.27 g/dL in women (p for trend <0.01) and with a mean difference of 0.21 g/dL in men (p for trend <0.01), compared to that at 0–200 m in 2021 dataset. Moreover, the proportion of women examinees with hemoglobin level <12.0 g/dL was 21.3% at 0–200 m and 17.6% at 600–800 m in 2021 (p for trend <0.01). These results were confirmed using the 2018 dataset.

CONCLUSIONS

As the residential altitude increased from sea level to 800 m, blood hemoglobin levels were slightly elevated, and anemia prevalence in women decreased, implying caution in hemoglobin measurements.

KEY WORDS

Anemia, hypoxia, altitude, hemoglobin

BACKGROUND

Blood hemoglobin (Hb) levels are influenced by age, sex, genetic background, lifestyle factors such as smoking habits, regular intake of vitamins and iron[1], and disease conditions[2,3]. In high-altitude residents, blood Hb levels increase due to barometric hypoxia-stimulated erythropoietin production in the kidneys[4]. This effect is commonly noted among highlanders, such as inhabitants in the Andean region[5–7], who acclimate to 2,500 m above sea level (masl) or higher[8]. Consequently, the impact of altitude on blood Hb levels has not been widely recognized as a confounding factor for regional Hb variations in lowland areas. However, recent studies have reported that Hb concentrations rise gradually from sea level to altitudes of 1,000–2,000 masl[9–11]. The World Health Organization states that Hb levels should be adjusted for elevation, noting that current cutoffs may under-adjust Hb levels for people residing at lower elevations and over-adjust Hb levels for people residing at higher elevations[12]. In this regard, clarification of Hb distribution in the low-elevation areas may impact on the diagnosis of anemia and polycythemia. Given that most of the population resides in the lowlands, the analysis would provide epidemiological insights for researchers and clinicians.

Herein, we hypothesized that blood Hb levels would significantly increase, even at altitudes lower than 1,000 masl, which can be detected in a cohort study with a sufficiently large sample size. Therefore, an ecological study is designed to take advantage of the nationwide adult health checkup system and the mountainous geometry of Japan, where approximately three-fourths of the national land is mountainous[13].

METHODS

STUDY DESIGN

Ecological study.

SETTING AND PARTICIPANTS

Participants comprised the general population aged between 40–44 years who were residing in Japan, and underwent annual nationwide Special Health Checkup in 2021 and 2018.

VARIABLES

Exposure is the altitude of the residential area. The main outcome was the mean Hb levels of the examinees in each secondary medical area. The secondary outcome measure was the proportion of examinees with low Hb levels.

DATA SOURCES/MEASUREMENT

Residential altitude was determined by the elevation above sea level of the city with the largest population in each secondary medical area, which was obtained from the maps issued by the Geospatial Information Authority of Japan[14]. Data regarding the blood Hb levels of the examinees were extracted from the annual nationwide Special Health Checkup in Japan as part of the NDB Open Data released by the Ministry of Health, Labour and Welfare[15,16]. The checkup was provided as a statutory obligation by insurers under the universal health coverage policy and implemented for the general population aged 40–74 years, with a coverage rate of 54.7% in 2018[17].

THE PROPORTION OF EXAMINEES WITH MEASUREMENT OF HB LEVEL

Hb levels were examined in individuals who were recommended by the physician to check the blood value, although the proportion of the examinees was not disclosed. Therefore, the rate was estimated using other aggregate tables that showed the distribution of body mass index, blood pressure, and triglyceride, which were mandated for the checkup examinees. The number of examinees was added to all the ranges for each items, and the maximum number was adopted as the total number of examinees.

HB LEVELS OF THE EXAMINEES IN EACH SECONDARY MEDICAL AREA

The NDB Open Data provides aggregated information based on 335 secondary medical area-based age groups with a five-year range. Because of the lack of an exact number of Specific Health Checkup examinees whose Hb data were used to calculate the mean Hb level, we referred to another aggregate table that showed the number of examinees in each range of Hb levels in each secondary medical area. The total number of examinees in each area was estimated by adding the number of examinees in all Hb ranges. In the NDB Open Data, values of 0–9 in the aggregate tables were masked for the sake of privacy, and these items were considered to be zero.

THE PREVALENCE OF THE EXAMINEES WITH LOW HB LEVELS IN EACH SECONDARY MEDICAL AREA

The NDB Open Data Japan showed the distribution of Hb levels categorized into three groups (Hb ≥13.1 g/dL, 12.1 g/dL ≤Hb ≤13.0 g/dL, Hb ≤12.0 g/dL for men, and Hb ≥12.0 g/dL, 11.1 g/dL ≤Hb ≤12.0 g/dL, Hb ≤11.0 g/dL for women). The proportion of female examinees having Hb ≤12.0 g/dL and male examinees having Hb ≤13.0 g/dL were focused on and calculated. Values from 0 to 9 in the aggregate table were masked; therefore, the missing values were estimated using the following steps. First, the national average prevalence of anemia was calculated from the data of 116 secondary medical areas without missing values. Therefore, the missing values were estimated as follows:

$$(\textit{estimated number of participants with anemia}) = \frac{(\textit{number of participants without anemia}) \times (\textit{average prevalence})}{(1 - \textit{average prevalence})}$$

If the estimated value was compatible with the missing value, representing a number between zero and nine, the value was adopted. Otherwise, either zero or nine was adopted; therefore, the number of examinees with anemia was the closest to the estimated value. There were no missing values in female datasets.

BIAS

Ecological fallacy.

STUDY SIZE

The study sample size was determined for all examinees all over the country, with blood Hb levels available in the database.

QUANTITATIVE VARIABLES

The residential altitudes of the 335 secondary medical areas were handled as an individual value or divided into four altitude groups: 0–199 masl, 200–399 masl, 400–599 masl, and 600–800 masl, which included 308, 14, 6, and 5 areas, respectively. In the latter method, the remaining two areas with altitudes of −0.8 masl and 801.6 masl were excluded from the analysis. Blood Hb levels in each secondary medical area were handled as the mean value of all the examinees or the proportion of examinees having Hb ≤12.0 g/dL or ≤13.0 g/dL for women or men, respectively, as stated above.

STATISTICAL METHODS

Alterations of the areal mean Hb levels or the proportion of the examinees with lower Hb levels in association of the residential altitude were assessed using the Jonckheere-Terpstra (J-T) test as a nonparametric test for trends[18]. Statistical significance was set at p <0.05. MATLAB, version R2022b (The MathWorks, Inc., Natick, MA, USA) was used for the biostatistical analysis.

ETHICAL COMMITTEE APPROVAL

The study was approved by the Institutional Review Board of the Graduate School of Medicine, University of Tokyo (#11612). Informed consent was not required because of the anonymous data of the Ministry of Health, Labour and Welfare as part of its nationwide program. The study protocol was designed according to the principles of the Declaration of Helsinki.

RESULTS

This study used the data from 1,207,304 women and approximately 1.74 million men aged 40–44 years, which is the youngest generation available in the database. The proportion of examinees with Hb levels evaluated was 64.6% and 71.4% of all examinees of the same sex and generation, respectively.

First, by analyzing the mean Hb levels of the examinees according to the altitude of the secondary medical area by citing the data for 2021, the mean Hb levels were found to be elevated in high-altitude areas in both women (**Fig. 1A**) and men (**Fig. 1B**). As for women, the Hb levels ranged from 12.5 g/dL to 13.1 g/dL. Areas where the mean Hb levels were ≤12.6 g/dL, ≤12.7 g/dL, and ≤12.8g/dL were all located at <200 masl, <400 masl, and <600 masl, respectively. Likewise, the Hb levels of men ranged from 15.1 g/dL to 15.6 g/dL, and areas where the mean Hb levels were ≤15.2 g/dL and ≤15.4 g/dL were all located at <200 masl and <600 masl, respectively. When secondary medical areas were categorized into four groups based on their altitude, the mean hemoglobin level at 600–800 m was elevated with a mean difference of 0.27 g/dL in women and with a mean difference of 0.21 g/dL in men, compared to that at 0–200 m. Also, the J-T trend test detected an upward trend in the mean Hb levels as the altitude increased in both women (J-T = 4.10, p <0.001, **Fig. 1C**) and men (J-T = 5.71, p <0.01, **Fig. 1D**).

To validate the results derived from the health checkup data for 2021, the health checkup data for 2018, which are the oldest data available, were analyzed. Mean Hb levels were found to be elevated in higher-altitude areas, and there was an upward trend in mean Hb levels as altitude increased in both women (J-T = 4.14, p <0.001) and men (J-T = 6.26, p <0.01). Collectively, these data suggest that blood Hb levels in the general population increase with increasing residential altitude.

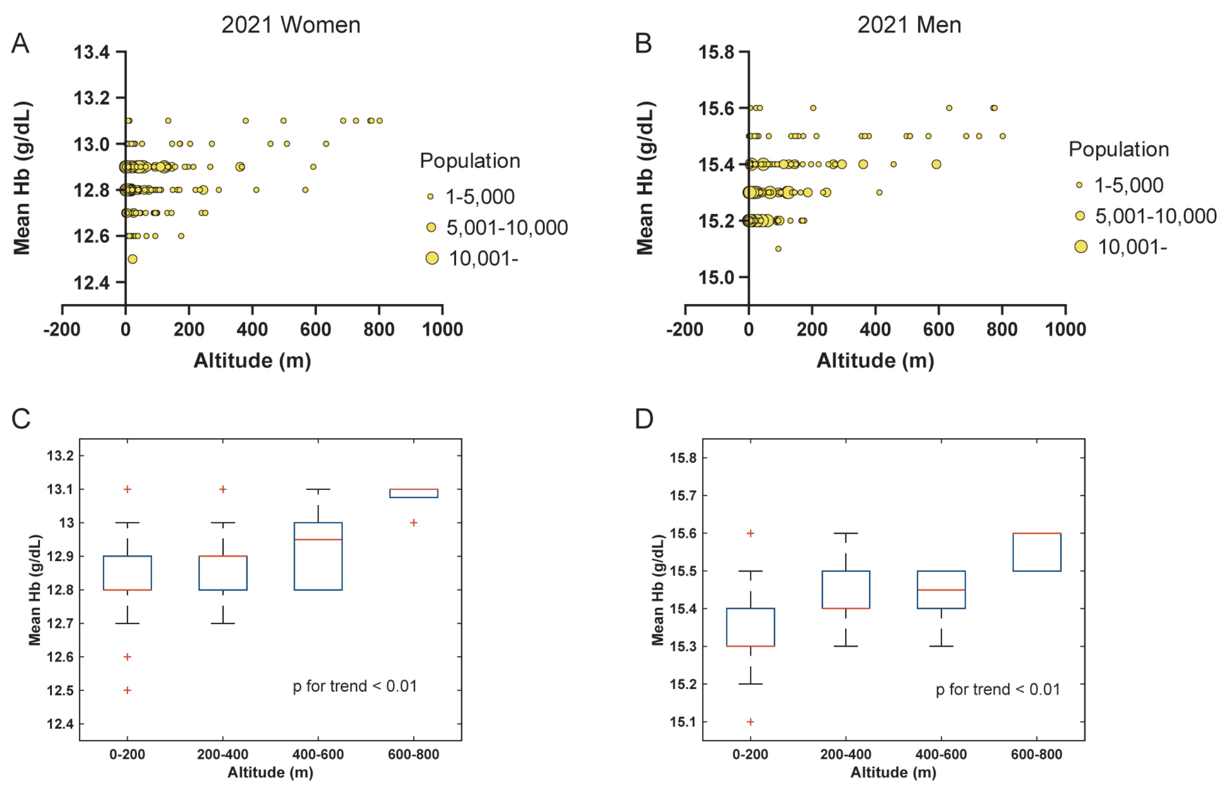

Fig. 1 Distribution of mean Hb levels of resident examinees by altitude in secondary medical areas of Japan

(A, B) Based on the available national health checkup data for 2021, a mean hemoglobin (Hb) level and an altitude in each secondary medical area were plotted for (A) women and (B) men. The size of yellow circles is determined by the sample size of the examinee population. (C, D) With secondary medical areas categorized into four groups by their altitude, a trend of mean Hb levels was evaluated using the Jonckheere-Terpstra trend test for (C) women and (D) men.

Next, we hypothesized that higher Hb levels with increasing altitude would result in a lower prevalence of anemia. Although anemia is generally defined with Hb ≤12.0 g/dL for women and ≤14.0 g/dL for men, due to the limited data availability in the database, the proportion of examinees with blood Hb levels ≤12.0 g/dL for women and ≤13.0 g/dL for men was focused on and calculated, and the relationship with altitude in each secondary medical area was analyzed. As for women, when the data were summarized in four altitude bands of 200 m each, the ratio of examinees with lower Hb concentrations gradually decreased from a mean of 21.3% at altitudes <200 masl to 17.6% at altitudes ≥600 masl (**Fig. 2A**). Regarding men, a significant decrease in the prevalence was observed only between the altitudes <200 masl and altitudes <400 masl ($\chi^2(1) = 19.8$, p <0.001, **Fig. 2B**). When the distribution of prevalence was analyzed in the four altitude bands, a significant downward trend was detected by the J-T trend test in both women (J-T = 3.54, p <0.001, **Fig. 2C**) and men (J-T = 3.14, p <0.001, **Fig. 2D**).

Then, these results were verified using the health checkup data for 2018. As for women, the ratio of examinees with lower Hb concentrations decreased from a mean of 21.9% at altitudes <200 masl to 19.6% at altitudes ≥600 masl, although a significant decrease was only detectable between the altitudes <400 masl and <600 masl ($\chi^2(1) = 8.97$, p = 0.003). Similarly, the prevalence of men with low Hb levels decreased from a mean of 1.10% at altitudes <200 masl to 0.91% at altitudes ≥600 masl, with a significant decrease observed between the altitudes <200 masl and <400 masl. ($\chi^2(1) = 7.53$, p = 0.006). When the prevalence was summarized in the four altitude bands of 200 m, a monotonic decrease in prevalence was observed in women (J-T = 2.81, p = 0.002), but not in men (J-T = 1.13, p = 0.13).

DISCUSSION

Our analysis indicated that an increase in residential altitude from 0 to 800 m positively affected blood Hb levels in both women and men in their early 40s. Fur-

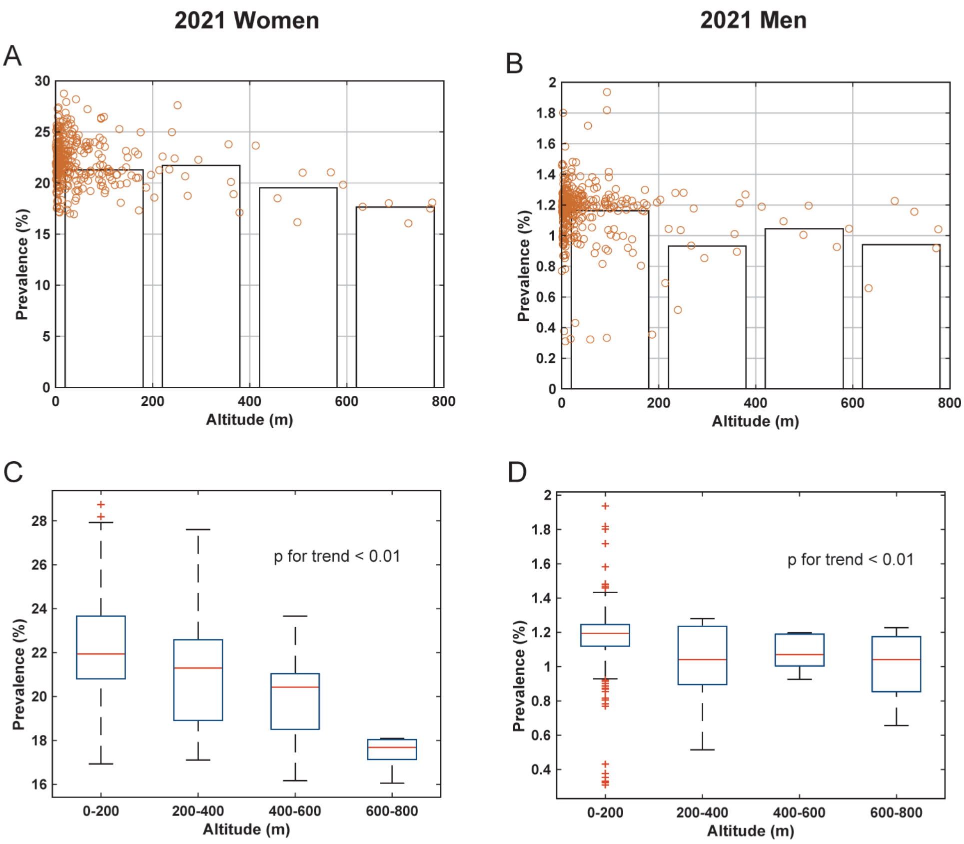

Fig. 2 Distribution of prevalence of examinees with low hemoglobin level by altitude in secondary medical areas of Japan

Based on the available national health checkup data of 2021, distribution of the prevalence of examinees with hemoglobin level of <12.0 g/dL for women and <13.0 g/dL for men in each secondary medical area. (A, B) Red circles indicate the altitude and the prevalence of (A) women and (B) men with low hemoglobin level in each secondary medical area. The white bars show the mean ratio of examinees with anemia in altitudes of 0–200 m, 200–400 m, 400–600 m, and 600–800 m. (C, D) With secondary medical areas categorized into four groups by their altitude, a trend of the prevalence of anemia was evaluated using the Jonckheere-Terpstra trend test for (C) women and (D) men.

thermore, the proportion of women examinees with anemia of Hb levels <12.0 g/dL decreased as altitude increased. The finding on Hb level distribution among men is consistent with a previous study on the younger male generation living at higher altitudes (0–2,000 masl) in Switzerland[11]. There are several possible explanations for the correlation between blood Hb levels and altitude at this lower range. First, although attention has been paid to barometric hypoxia primarily in the Andes highlands, previous studies have pinpointed a negative linear relationship between barometric pressure and the partial pressure of arterial oxygen (PaO_2) even at an altitude of 0–1,400 masl[19,20]. Based on a classical equation[21], in dry air, PaO_2 at 800–1000 masl is estimated to be 136 mmHg, which is lower than 147 mmHg at sea level. Therefore, erythropoietin-producing cells in the kidney may sense this slight decrease in PaO_2, leading to enhanced erythropoietin production. Secondly, serum ferritin levels reportedly increase with altitude[11,22], which may explain the lower prevalence of iron deficient anemia at higher altitudes. Although serum ferritin levels are modulated by many factors, barometric hypoxia alone, in theory, promotes iron absorption independent of Hb levels via the up-regulation of iron transporter genes, possibly leading to an increase in iron storage[23].

The clinical significance of the magnitude of the blood Hb level gradient at 0–800 masl should be carefully considered, even if the numerical difference shows a statistically significant level of $p < 0.05$[24]. In other words, scientific conclusions should not be based only on whether a p-value passes a specific threshold[24]. The Hb level increase we found was as small as <1.0 g/dL per 800 m; however, this unobtrusive gradient might affect the normalization of the laboratory values between countries and areas. Indeed, the World Health Organization recommended adjustments of Hb concentrations to diagnose anemia at every 500 m to account for the effect of elevation of place of residency on Hb concentrations[12]. Clinical research to update this Hb adjustment is currently underway[25]. Our results provide novel insights in this regard.

Our study had a few limitations. First, blood ferritin levels and transferrin saturation, which affect Hb levels, were not included in the national health checkups. Second, the ratio of examinees whose Hb levels were measured among all residents may differ between secondary medical areas, making it difficult to perform a completely accurate estimate of the Hb levels of all residents in each area. This limitation cannot be avoided if the checkup is based on spontaneous participation; however, the actual coverage ratio was not as small as mentioned above. Third, a Hb level of 13.0 g/dL was employed as the cutoff level for men, although the standard Hb value for men is usually 14.0 through 18.0 g/dL. This is because NDB Open Data does not distinguish Hb level of >13.0 g/dL. In contrast, the standard Hb value is usually 12.0–16.0 g/dL for women, and a cutoff of 12.0 g/dL was used, which would provide more clinically relevant results in terms of the diagnostic criteria of anemia. Moreover, for men, approximately one-third of secondary medical areas lack the exact number of examinees with low Hb levels owing to the database policy. Furthermore, this calculation was adopted to possibly underestimate the gap in anemia prevalence by altitude to avoid a false-positive correlation. Even under these rather strict conditions, a decrease was observed in the prevalence of anemia in the 0–200 m and 200–400 m altitude ranges.

CONCLUSIONS

The nationwide health checkup data in Japan, a mountainous archipelago, show a slight but significant elevation in blood Hb levels in the general population in accordance with residential altitude. These results suggest that barometric hypoxia may elevate the blood Hb levels of residents at these altitudes. When blood Hb concentrations are evaluated, the variation in altitude should be considered even unless people reside in continental high mountains such as the Andes or Alps region. These data warrant further investigations to clarify the mechanisms underlying the modulation of blood Hb levels at different altitudes. Ideally, a survey to evaluate not only Hb concentrations but also iron dynamics and vitamin levels among the sufficiently large general population residing uniformly with a low-altitude range would be conducted.

CONFLICT OF INTEREST STATEMENT

H.N. received research grants from Bayer, Boehringer Ingelheim, Kyowa Kirin, Mitsubishi Tanabe, and Novo Nordisk outside the scope of the submitted work and honoraria from Astellas, Astra Zeneka, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, Kowa, Kyowa Kirin, MSD, Mitsubishi Tanabe, Ono, Ostuka, and Torii outside the scope of the submitted work. M.N. received research grant from Boehringer Ingelheim outside the scope of the submitted work. The remaining authors have no conflicts to disclose.

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