

## ORIGINAL ARTICLE

# Hemoglobin Concentration Reference Interval Revisited: a Nationwide Study from Korea

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### SUMMARY

**Background:** Anemia is a common cause among the elderly for increased mortality. Hemoglobin concentration can be affected by many factors, but the reference interval defined by the World Health Organization has not been adjusted for the previous half century.

**Methods:** Through using the dataset generated by the National Health Insurance (NHI) health screening program of Republic of Korea, here we attempt to present a close to actual hemoglobin concentration of the Korean population. Between January 2009 and December 2013, a total of 57,409,872 health screening events were registered in the NHI database. Following the exclusion criteria, 6,759,566 participants were enrolled for analyses.

**Results:** Significant portion of the study population was considered 'anemic', while the mean value (2.5% ~ 97.5%) of hemoglobin concentration from the study was 14.8 (12.5 ~ 16.8) g/dL in men and 12.8 (10.6 ~ 14.7) g/dL in women. Concordant results of hemoglobin concentration declining with age were observed as previous studies have described, supporting the need for separate, possibly lower cutoff in the elderly.

**Conclusions:** A considerable portion of the participants being categorized as anemia contests the accuracy of the current lower cutoff for anemia. From a large representative dataset, the need for adjustment to the lower cutoff for anemia is suggested.

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#### KEY WORDS

hemoglobin, reference interval, anemia, big-data, national

## INTRODUCTION

Anemia is a common condition in the elderly, typically defined by the World Health Organization (WHO) criteria as hemoglobin concentration below 13 g/dL in men and 12 g/dL in women [1]. Previous comprehensive studies have demonstrated the increasing prevalence of anemia among the elderly, which resulted in increased mortality and elevated burden of healthcare expenditure [2-4]. Meanwhile the definition of anemia, adopted for almost 50 years, is basically a statistical distribution from a reference population, and the need for adjusting the cutoff for the anemic elderly in association with increasing comorbidities has been raised [3,4]. A large database such as the National Health and Nutritional Examination Survey (NHANES) has been used as a comprehensive database to successfully determine the prevalence of anemia among certain populations [5], as hemoglobin concentration is affected by numerous factors such as age, gender, nutritional status, underlying diseases, and ethnicity [6]. The National Health Insurance (NHI) program is a nationwide compulsory health care system supervised by the Ministry of Health and Welfare of the Korean Government capable of generating representative data of the Korean population [7]. The aim of this study is to present a close to actual hemoglobin concentration reference interval of Korean population using the largest dataset so far, generated by the NHI health screening program.

## MATERIALS AND METHODS

### Study design

Information from the NHI database between January 2009 and December 2013 were used. A total of 57,409,872 health screening events were registered during the period. The latest data within the same year was used from those who participated more than once in a year, registering with their latest data within that year. Figure 1 is a flow diagram summarizing the study design. The exclusion criteria included previously diagnosed diseases (respiratory diseases including tuberculosis, hypertension, obesity, anemia, diabetes mellitus, dyslipidemia, liver diseases, kidney diseases), smoking, alcohol consumption of more than twice a week, pregnancy, and past medical history (stroke, any heart related condition, cancer/malignancy, and hepatitis B carrier status). This study design and its retrospective use of data was approved by the Institutional Review Board of the National Health Insurance Service Ilsan Hospital (IRB No. NHIMC 2016-11-019).

### Statistical analyses

Data were analyzed across age groups in men and women, categorized by 10 years. Yearly changes in hemoglobin concentration were analyzed in men and women for each respective age group. Reference intervals for hemoglobin concentration are presented using mean

value with 95% confidence interval (CI) and median value with 2.5 ~ 97.5 percentiles. All statistical analyses in this study were done using SAS v 9.4 (SAS Institute Inc., Cary, NC, USA).

## RESULTS

Distribution of study participants and proportions of each age group among all participants are portrayed in Figure 2. The total number of enrolled participants of the NHI health screening program was 6,759,566, comprised of 1,702,625 men and 5,056,941 women. After applying exclusion criteria, 11.8% were enrolled. More frequent presence of smoking and alcohol consumption over twice a week resulted in a disproportionate exclusion of men.

Yearly analysis of hemoglobin concentration from 2009 to 2013 is shown in Figure 3. Negative correlation between hemoglobin concentration and age is apparent (hemoglobin decreasing with age); however, the mean hemoglobin concentration was observed to increase annually, except for the 70s.

The reference interval for hemoglobin concentration of Korean population in this study is illustrated in Figure 4. The reference interval for the whole study population using a median value (2.5 ~ 97.5 percentile) was 14.8 (12.5 ~ 16.8) g/dL in men and 12.8 (10.6 ~ 14.7) g/dL in women. The difference in hemoglobin concentration between men and women was more than 2 g/dL in age groups under 40s, and this gap narrows after reaching the 50s. Notably the hemoglobin concentration in women declines from the 20s to the 40s, and then rebounds up in the 50s where the declining continues.

## DISCUSSION

The WHO definition of hemoglobin concentration cutoff for anemia is 13 g/dL in men and 12 g/dL in women. From our study of Korean population, the median values were 14.8 (12.5 ~ 16.8) g/dL in men and 12.8 (10.6 ~ 14.7) g/dL in women, in which significant portions of men over 40s and women of all ages can be considered anemic. Previous studies have raised concerns about the increasing burden of anemia among elderly population, estimating the prevalence of anemia in elderly at around 10% [8-10]. Observations from this study deviate from this estimation and are also contradictory to the most recent and world-wide analysis of global anemia burden, observing the most reduction of anemia burden in East Asia, where Korea is located [11]. The yearly increase of hemoglobin concentration seen in most age groups is a consistent finding with the global analysis (Figure 3). The accuracy of the reference interval for hemoglobin concentration was found questionable based on the findings of the study, comparing favorably with the previous suggestions from Sweden raising the need for cutoff adjustment according to age groups, because 28% of the

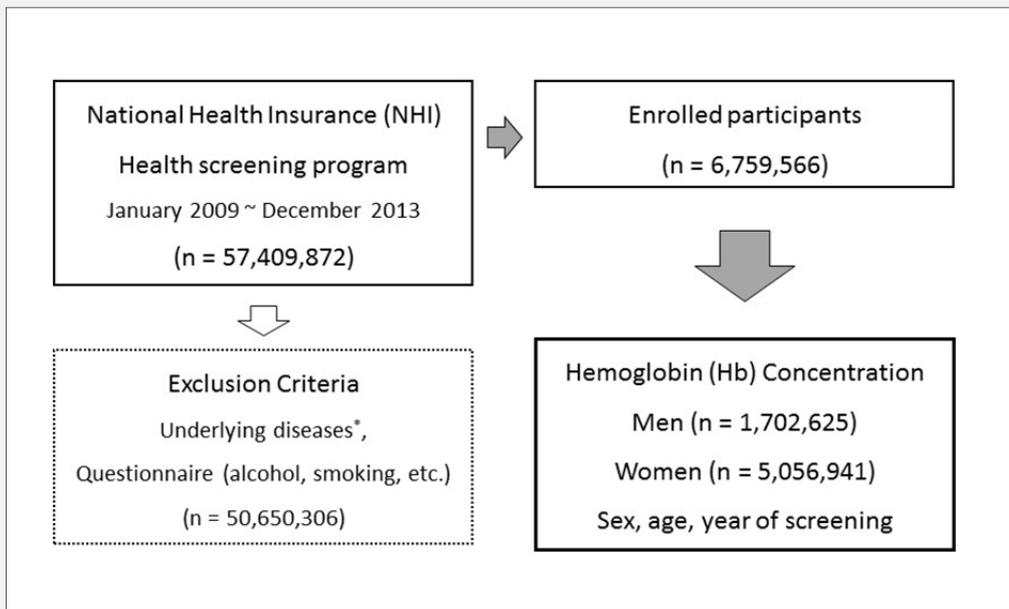


Figure 1. Study design and enrolled participants after applying exclusion criteria.

\* - Underlying diseases; respiratory diseases including tuberculosis, hypertension, obesity, anemia, diabetes mellitus, dyslipidemia, liver diseases, nephrotic diseases.

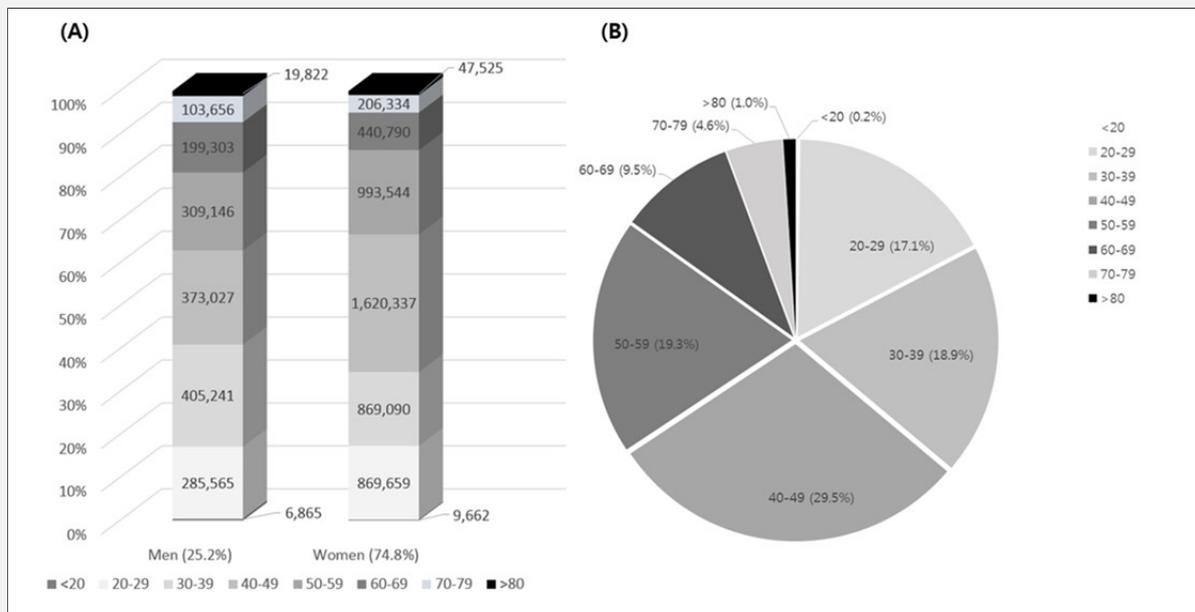


Figure 2. Distribution of study participants among age groups in men and women (a) and the proportion of age groups from total study participants (b).

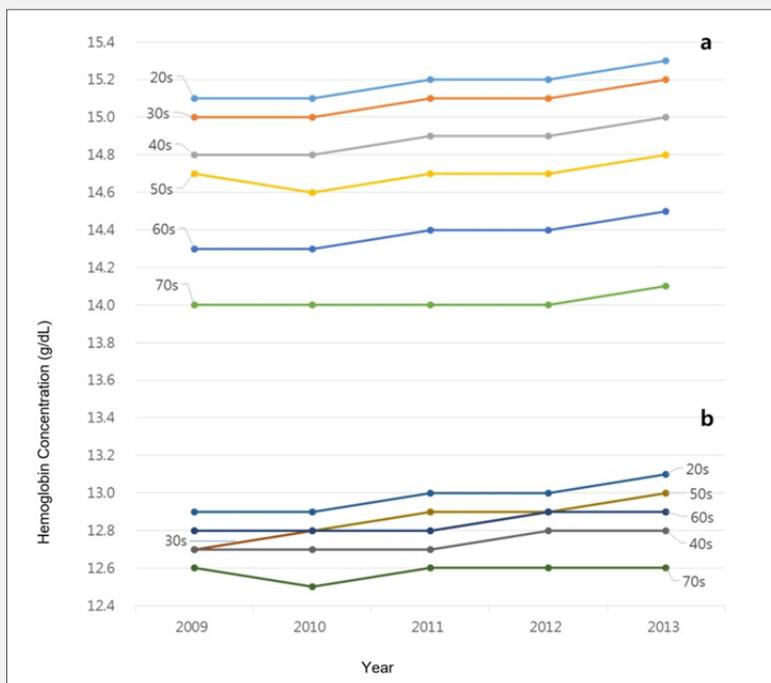


Figure 3. Chart showing yearly changes of mean hemoglobin concentration in (a) men and (b) women.

Hemoglobin concentration of Korean population increases slightly overall within the study period (Women 30s overlaps with Women 60s between 2010 and 2013).

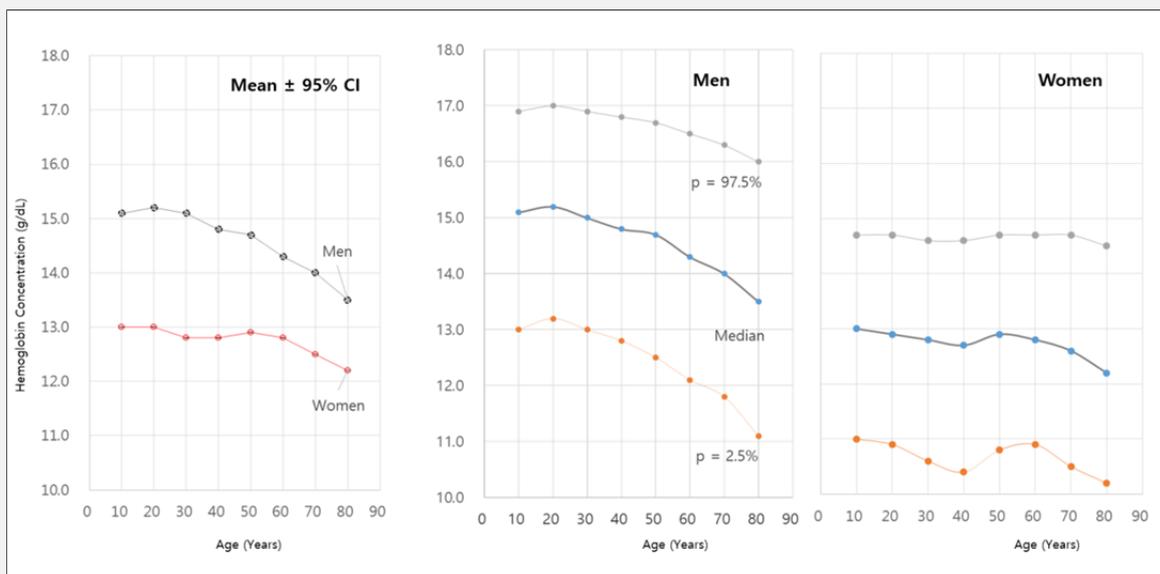


Figure 4. Age dependent reference interval for hemoglobin concentration of Korean population.

population was anemic by the WHO definition [3]. Hemoglobin concentration range differs between men and women, in which women are considered more vulnerable to anemia relating to iron deficiency. However, findings from this study suggest that men are also vulnerable to anemia when aging as hemoglobin concentration declined more in men (1.7 g/dL) than women (0.8 g/dL) between the 20s and 80s (Figure 4). A study from Taiwanese population also reports a higher prevalence of anemia among men using the WHO criteria, and additionally a higher mortality risk in older men [2]. The high prevalence of anemia in men may have resulted from the higher hemoglobin concentration cutoff, but the clinical implications of these differences in men and women are yet to be clearly determined.

While two thirds of anemia is attributable to nutrient deficiency and chronic inflammation, this leaves the cause of one third as 'unexplained' [8]. In this study, participants of the NHIS health screening program were screened with exclusion criteria that cover most causes of anemia, except 'unexplained'. Many more causes of anemia exist and also unexplained anemia may not have been excluded from the population in this study, but the accuracy of the lower cutoff for anemia is arguable, at least for the Korean population. Anemia, especially in mild forms, should be considered more than a decrease in hemoglobin concentration and taken as a warning sign for underlying causes.

Hemoglobin concentration decreasing with age is well established and expected upon the fifth decade of life according to a study from the United States [8]. A decrease of hemoglobin concentration in this study was apparent from the 30s, which, in our opinion, was interesting. Explanation for this early decrement may be attributed to different socio-economic backgrounds among age groups. Subjects were born between 1930 and 1993, during which generations have experienced vastly different economy and hence different medical care, resulting in differences of physical conditions, mostly improvements, towards younger generations. A study from closely neighboring Japan demonstrated that a cohort of younger generation subjects, from the Hiroshima and Nagasaki area born in 1945, had higher hemoglobin levels than the past generation born in 1895 when compared at the same age [11]. To verify this difference in this study, a cohort from this study requires further verification through follow-up research when each age group becomes of the corresponding age.

A key aspect of this study is the representativeness of the Korean population by utilizing significantly large number of participants from the NHIS health screening program. High participation rate (76.1% in 2015, data not shown) of the program attributes representativeness of the Korean population. Availability of integrated disease information providing clinical data (i.e., medical history) is also a comparable aspect of this study to other laboratory data-based analyses. Limitations of this study may include lack of data describing the uniformity of instruments used for measurement of hemoglobin,

in which 3,994 government designated health screening institutions as of 2010 have conducted these measurements. The national health insurance only reimburses for measurements using the cyanmethemoglobin method or its equivalent, in which certain level of uniformity can be expected. Medical laboratories currently operating in Korea are subject to quality assurance and external quality control programs since 1999. As of 2013, 1,271 institutions participated with the external quality control program operated by the Korean Association of External Quality Assessment Service (<http://www.labqa.org>) [12]. The Laboratory Medicine Accreditation Program standards accredited by the International Society for Quality in Health Care (ISQua) also ensures the quality and uniformity of the laboratory testing services provided in Korea.

From this study of hemoglobin concentration of representative data from Korean population, the lower cutoff for anemia of < 13 g/dL for men and < 12 g/dL for women may incorrectly reflect the prevalence of anemia among population. The necessity of age group adjusted criteria was noticed, especially regarding the elderly as population aging is one of the nation's largest concerns. Although anemia manifests simply as decreased hemoglobin concentration, the pathophysiology and epidemiology are complex and findings of this study may only represent the tip of the iceberg. Further studies incorporating the actual burden of anemia on the population are required to confront this yet under-recognized condition.

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#### **Author Contribution:**

J. J. Y and Y. J. K contributed equally to this work. J. Y and T. S. P are co-correspondence authors for this work.

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#### **Declaration of Interest:**

All authors declare no conflicts of interest regarding this article. This work was supported by the National Health Insurance Service Ilsan Hospital Grant (NHIS-2017-1-116) to J. Y. No other funding sources exist. NHIS had no involvement in article preparation.

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