High Anemia Prevalence in Korean Older Adults, an Urgent Healthcare Problem: 2007-2016 KNHANES

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Running Title: High Anemia Prevalence in Korean Older Adults

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ABSTRACT

BACKGROUND: Anemia is associated with high morbidity and mortality in older people. However, anemia in older individuals is not fully understood, and national data on the prevalence and characteristics of anemia in Korean older people are lacking. This study aimed to evaluate the prevalence and characteristics of anemia in older adults using data from the Korea National Health and Nutrition Examination Survey (KNHANES) , which is the nation-wide cross-sectional epidemiological study conducted by Korean Ministry of Health and Welfare.

Methods: Data from the total of 62,825 participants of the 2007-2016 KNHANES were merged and analyzed to investigate differences in participant characteristics and potential risk factors for anemia.

RESULTS: The prevalence of anemia was higher in the population aged ≥65 years (older adults) than in the younger population. Anemia was also more prevalent among females than among males, but the difference was not statistically significant in people aged >85 years. Being underweight, receiving a social allowance, living alone, and having comorbidities such as hypertension, arthritis, diabetes mellitus (DM), cardiovascular disease (CVD), stroke, cancer, and chronic renal failure (CRF) were more prevalent in older adults with anemia than in the group without anemia. In the univariate and multivariate analyses, older age, female sex, underweight, and comorbidities including arthritis, DM, CVD, stroke, cancer, and CRF were associated with an increased risk of anemia. Furthermore, the prevalence data were significantly higher in this study than in previous studies.

CONCLUSIONS: This study revealed that age, female sex, underweight, and the presence of comorbidities such as arthritis, DM, CVD, stroke, cancer, and CRF were associated with an increased risk of anemia in Korean older adults. Our findings may be useful in developing

interventions and programs aimed at healthy aging. Further study on causal relationships between anemia and other variables in the older population is necessary.

Trial registration: KNHANES was approved by the KCDC Research Ethics Review Committee annually since 2007(2007-02CON-04-P, 2008-05EXP-01-C, 2009-01CON-03-2C, 2010-02CON-21-C, 2011-02CON-06-C, 2012-01EXP-01-2C, 2013-07CON-03-4C, 2013-12EXP-03-5C, 2015-01-02-6C). Ethical approval of this study was obtained through the Institutional Review Board of Dong-A University Hospital (DAUHIRB-EXP-20-035).

Keywords: anemia; older adult; KNHANES; comorbidity

Availability statement: The datasets generated and/or analyzed during the current study are available in the KHNANES repository, https://knhanes.cdc.go.kr/knhanes/eng/index.do

Abbreviation: *KNHANES* Korea National Health and Nutrition Examination Survey, *DM* diabetes mellitus, *CVD* cardiovascular disease, stroke, cancer, and *CRF* chronic renal failure

INTRODUCTION

The prevalence of anemia is known to increase with age. A previous epidemiological study in the U.S. showed that anemia was prevalent in >10% of people aged ≥65 years (older adults) and in >20% of those aged ≥85 years[1]. According to the 2018 National Health Statistics for Korea, the prevalence of anemia in men and women aged 60-69 years was 5.3% and 8.0%, respectively, and in those aged >70 years, the prevalence was higher, at 16.4% and 18.3%, respectively[2]. Anemia in older adults is reported to be mainly due to nutritional deficiency following chronic kidney disease, blood cell disorders, and other diseases[3, 4]. However, the etiology of anemia is unclear in a certain percentage of individuals, despite various tests being conducted in this group, including bone marrow aspiration and biopsy[1, 5, 6].

Anemia in older people has been reported to be more prevalent in individuals who are staying in nursing homes and who are hospitalized[7-10]. Several studies also noted that anemia in the older population is related to various medical burdens, including increased morbidity and mortality[11] . In particular, anemia has been reported to be related to higher cardiovascular events[12, 13], frailty[7, 14, 15], fractures[16], prolonged hospital stay, and unfavorable outcomes[17-19]. However, anemia in older people is not fully understood. Although previous studies have shown chronic kidney disease, nutritional deficiency, and malignancy as the major causes of anemia[3, 4, 9], the cause of anemia in some populations remains unknown.

The population of older people in many developing and developed countries, including South Korea, is increasing. In South Korea, the average life expectancy is increasing, while the birth rate per woman is decreasing. According to Statistics Korea, the proportion of older adults in South Korea was 14.3% in 2018 and is predicted to rise to 46.5% in 2067[20]. Despite these findings, the social and health policies and provisions for older people in Korea are inadequate.

In this regard, this study aimed to evaluate the actual prevalence of anemia in older adults in South Korea and elucidate the burden of health problems related to anemia, using data from a large nationwide survey.

METHODS

Study Population and Characteristics

This study used data from the Korea National Health and Nutrition Examination Survey (KNHANES). The KNHANES is a nationwide health and nutrition survey designed by Korea Centers for Disease Control & Prevention, and conducted annually by the South Korean government according to the Article 16 of National Health Promotion Act. The survey was first conducted in 1998, and its structure and format have substantially evolved since 2007. The survey includes questionnaire items and details of laboratory tests, which have been regularly revised every 3 years. For reasons of data homogeneity, this study merged and analyzed data from the KNHANES conducted from 2007 to 2016.

The participants of the KNHANES include community-dwelling Koreans carefully selected by statistical methods that use multivariable stratification and cluster sampling to represent the entire Korean population. The survey excludes individuals from military troops, prisons, hospitals, and nursery or social homes. Participants are selected and reenrolled as family units to gather complete data on all family members. Written informed consent is obtained from the participants at the start of each survey examination. Personal data and results of the survey are de-identified before they are made publicly available.

In this study, we used data from the latest 10 years of the survey. Repetitive participants were excluded in the original survey examination. To analyze the etiologies of anemia, only data from 2010 to 2012 were used because it was only during that period that serum iron, serum

total iron-binding capacity (TIBC), and ferritin were included as laboratory survey items. KNHANES survey examination study was approved by the Korean Centers for Disease Control & Prevention Research Ethics Review Committee, and gaining renewal annually. Ethical approval of this study was obtained through the Institutional Review Board of Dong-A University Hospital.

Definition of Terms

Anemia was defined as a hemoglobin level of <13.0 g/dL for men and <12.0 g/dL for women, based on the World Health Organization criteria for anemia. Underweight was defined as a body mass index of <18. Household income was initially classified into four categories, and the lowest household income was defined as "low household income." Under the item "food insecurity," "insecurity" was defined as having the following answer: "have trouble often or frequently in having adequate amount and quality of daily food for economic reason." Comorbid conditions were defined as those diagnosed by a doctor, as reported by the participant. Hypertension referred to a resting systolic blood pressure of >140 mmHg or a diastolic blood pressure of >90 mmHg at examination. Diabetes mellitus (DM) was defined as having been diagnosed with DM or treated for DM or having a fasting blood glucose level of >126 mg/dL. Chronic renal failure (CRF) was defined as an estimated glomerular filtration rate of <60 mL/min using the Modification of Diet in Renal Disease Study equation.

Statistical Analysis

The KNHANES has specific guidelines for statistical analysis, including cluster sampling and stratification, to ensure accuracy of data [21]. To represent the entire Korean population, the sampling weights assigned to the participants were applied to all analyses and were generated

taking into account the complex sample design, nonresponse rate of the target population, and post-stratification. Differences in participant characteristics were compared across subgroups using the chi-squared test for categorical variables and independent *t*-test for continuous variables, as appropriate. Univariate and multivariate analyses using logistic regression were performed to identify prognostic factors that were independently related to anemia in older adults. As hemoglobin itself can be used to show significant differences between participants with and without anemia, this variable was removed during the multivariate analysis. The prevalence of anemia was plotted by age and sex for data visualization. All statistical analyses were carried out using IBM SPSS® Statistics version 24.0 (IBM, Armonk, NY). A two-sided *P*-value of <0.05 was considered statistically significant.

RESULTS

The data of 81,503 participants in the 2007-2016 KNHANES were retrieved. Among the participants, 18,678 were excluded from this study because of missing laboratory data. Thus, a total of 62,825 participants were included in the analysis, of whom 12,519 were aged ≥65 years (Figure 1). The age distribution was analyzed according to the survey periods. A trend of increase in the proportion of older adults was observed but was not statistically significant (Figure 2).

Prevalence of Anemia

Of the 62,825 participants, 5,315 had anemia, including 1,024 males and 4,291 females. The overall prevalence of anemia in the population aged ≥10 years was 7.3% (95% confidence interval [CI], 7.1%-7.5%). The prevalence of anemia in the population aged ≥65 years was

14.0% (95% CI, 13.3%-14.7%), whereas that in the population aged <65 years was 6.4% (95% CI, 6.2%-6.6%). The prevalence of anemia was higher in females (12.2%; 95% CI, 11.8%-12.6%) than in males (2.5%; 95% CI, 2.3%-2.7%). However, in the population aged >85 years, the prevalence of anemia between men and women did not show any significant difference (26.6% vs. 22.5%, $P = 0.577$; Figure 2).

Difference in Characteristics Between Older Adults With and Without Anemia

The baseline characteristics of older adults with and without anemia are shown in Table 1. Known risk factors for anemia were included as variables in the analysis. The population with anemia had a lower mean hemoglobin level, older age, and higher proportion of women. The group with anemia also showed a higher proportion of participants who were underweight, were beneficiaries of social allowance, and who were living alone than the group without anemia. No statistical differences in household income or food insecurity were observed. Moreover, the population with anemia tended to have a higher prevalence of hypertension, arthritis, DM, stroke, cancer, and CRF (Table 1).

Relationships between independent and dependent variables were analyzed using univariate and multivariate logistic regression. The analysis of risk factors for anemia in older adults is shown in Table 2. The mean hemoglobin levels were not included in further analysis due to the definite differences in hemoglobin levels between participants with and without anemia. Based on the results, the risk of anemia increased with older age (odds ratio [OR], 1.057; 95% CI, 1.045-1.070; $P < 0.001$) and with female sex (OR, 1.270; 95% CI, 1.097-1.471; $P = 0.001$). Underweight (OR, 2.263; 95% CI, 1.622-3.157; $P < 0.001$), arthritis (OR, 1.174; 95% CI, 1.017-1.354; $P = 0.028$), DM (OR, 1.419; 95% CI, 1.229-1.638; $P < 0.001$), cardiovascular disease (CVD) (OR, 1.396; 95% CI, 1.123-1.737; $P = 0.003$), stroke (OR, 1.344;

95% CI, 1.020-1.772; $P = 0.036$), cancer (OR, 2.738; 95% CI, 1.937-3.870; $P < 0.001$), and CRF (OR, 2.513; 95% CI, 2.174-2.904; $P < 0.001$) were also associated with an increased risk of anemia.

Analysis of the Etiologies of Anemia Using the 2010-2012 KNHANES Data

The etiologies of anemia were analyzed using data from the 4th KNHANES, which was conducted from 2010 to 2012 (Table 3). Only during this period were serum iron, TIBC, and ferritin included as survey items. The overall prevalence of anemia in this period was 7.0% (95% CI, 7.0-8.0). In the group with participants aged <65 years, the prevalence of anemia was lower (6.0% [CI 95%, 6.0-7.0%] vs. 14.0% [CI 95%, 12.0-15.0%], $P < 0.001$), but the prevalence of having a hemoglobin level of <10.0g/dL was significantly higher (1.10% [CI 95%, 0.09-0.13] vs. 0.88% [CI 95%, 0.5-1.26%], $P < 0.001$).

Among older adults with anemia, the percentage of those with iron-deficiency anemia (IDA) was lower ($P < 0.001$), while the percentages of those with cancer, DM, hypertension, CRF, stroke, CVD, and arthritis were higher (cancer: $P = 0.026$, all others: $P < 0.001$). The proportion of participants with other nutritional deficiency disorders could not be analyzed because the levels of other nutrients were not included in the survey. In the risk analysis, the estimated OR was 2.747 (95% CI, 2.334-3.234; $P < 0.001$) when comorbidity was considered as a numeric variable, and participants who had more than three comorbidities showed a higher risk of anemia (OR, 16.535; 95% CI, 9.768-27.989; $P < 0.001$).

DISCUSSION

The occurrence of anemia in older people is not fully understood. Hemoglobin levels in the older population are reportedly lower than the reference values for other population groups.

Reference values represent average levels with standard deviations, and the low hemoglobin levels in the older population might be considered as the standard reference values for this population group. Some reports concluded that this decrease in hemoglobin levels might be one of the consequences of the normal aging process; hence, the criteria for anemia should be different in this population[17, 22-25]. However, many reports also showed that anemia in older persons is related to the presence of underlying health conditions and is therefore associated with high mortality and morbidity. Furthermore, most people with anemia have been shown to have nutritional deficiency, but the etiology is unknown in one-third of anemia cases[3, 26]. This unexplained category of anemia includes aging-related clonal hematopoiesis (ARCH), idiopathic cytopenia of undetermined significance (ICUS), and pre-myelodysplastic syndrome (MDS); these conditions are associated with a low but potential risk of hematologic malignancy[5, 6, 27]. Therefore, older people with anemia are recommended to undergo evaluations for etiology analysis[6]. However, there is no guideline or consensus for the range and frequency of the evaluation and management of this population.

In this study, the prevalence of anemia ranged from 12% to 17%. These differences might be attributed to the diversity of the subjects and cohorts[3, 8, 23, 25, 28]. Studies conducted in nursing home- and hospital-based populations have shown significantly higher prevalence of anemia and morbidity. However, most of these studies seem to show similar findings with regard to the prevalence of anemia in older adults—that is, the prevalence of anemia tends to increase with age, and there is no sex difference, with some studies even showing a higher prevalence of anemia among males. In particular, a study in the U.S. showed that in people aged >85 years, the prevalence of anemia was higher among males[3].

The prevalence of anemia in older adults reported in this study is significantly higher than that in other epidemiological reports. This finding is quite striking because this study was

based on populations who were relatively healthy and lived in a secure environment. Besides, it is expected that the prevalence of anemia would be much higher in those who live in a less secure environment, are admitted in hospitals or social facilities, and experience malnutrition due to financial reasons. Studies in admitted patients and people with diseases have shown that anemia is associated with a high risk of complications and poor outcomes.

This study showed that older adults with anemia were underweight, which might be related to malnutrition. However, this finding is inconsistent with those of previous studies showing that being a beneficiary of social allowance or having a low household income is not a risk factor for anemia. This nationwide survey did not include any other specific data for malnutrition aside from body weight. Further study is thus required to clarify the relationship between anemia and malnutrition.

This study also showed that anemia might be related to various underlying conditions. We found that the risk of anemia increased as the number of comorbidities increased. In addition, the proportion of participants with IDA was lower among older adults than in the younger population. However, this study is limited in that the KHNANES data cannot be used to show a causal relationship between variables. To determine the cause-and-effect relationship between these variables, large well-designed prospective cohort studies are necessary. Another limitation is that the questionnaire items of the KHNANES are being revised every 3 years for economic reasons, making it impossible for researchers to investigate the possible etiologies of anemia in the study population. As the etiologies of anemia seem to be more complicated in older adults than in the younger population, anemia may pose a heavy medical burden on older people in countries such as South Korea.

In conclusion, this study revealed that age, female sex, underweight, arthritis, diabetes, CVD, stroke, cancer, and CRF were associated with an increased risk of anemia among older

adults in South Korea. Compared with the younger population with anemia, older adults with anemia had higher incidences of cancer, DM, hypertension, CRF, stroke, CVD, and arthritis but a lower incidence of IDA. Our findings will be very relevant to developing interventions and programs aimed at healthy aging at the individual and societal levels.

Abbreviations

KNHANES Korea National Health and Nutrition Examination Survey, *DM* diabetes mellitus, *CVD* cardiovascular disease, stroke, cancer, and *CRF* chronic renal failure, *TIBC* total iron-binding capacity, *IDA* iron-deficiency anemia, *ARCH* aging-related clonal hematopoiesis, *ICUS* idiopathic cytopenia of undetermined significance, and *MDS* pre-myelodysplastic syndrome

Competing interests

The authors declare no conflicts of interest.

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Author Contributions

HW Chueh and JY Han designed the study. HW Chueh performed the statistical analysis. HW

Chueh and JY Han wrote the manuscript, and HL Jung, YJ Shim, and HS Choi reviewed the final draft. All authors read and approved the final manuscript.

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Authors' information

Corresponding author Jin Yeong Han is laboratory hematologist who have contributed to improvement of laboratory medicine in Korea, especially in hematologic division in laboratory medicine. She is very interested in congenital and acquired red blood cell disorders, and has served as the chair of the Red Blood Cell Working Party in Korean Society of Hematology. Recently she is having interest in laboratory problems in elderly populations. First author, Hee Won Chueh is the pediatric hematologist, and have reported many works in general hematology based on big data. She is interested in anemia and other common red blood cell disorders, and actively participate in the Red Blood Cell Working Party in Korean Society of Hematology. Other authors, Hye Lim Jung, Ye Jee Shim, and Hyoung Soo Choi are pediatric hematologist who actively participating the Red Blood Cell Working Party in Korean Society of Hematology. Especially, Hye Lim Jung and Hyoung Soo Choi also served as chairman of Red Blood Cell Working Party, and reported many works on anemia and blood cell disorders.

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TABLES

Table 1. Comparison of Baseline Characteristics of Older Adults With and Without Anemia

Variable	Older Adults With Anemia (n = 4,444,812.928)	Older Adults Without Anemia (n = 699,077.287)	*P*-Value
Mean age, years	71.96 ± 0.06	74.00 ± 0.15	<0.001*
Women, %	55.1 ± 0.5	61.8 ± 1.3	<0.001†
Mean Hb level (SE)	14.00 ± 0.01	11.48 ± 0.03	<0.001*
Underweight (BMI < 18), %	2.0 ± 0.2	4.5 ± 0.6	<0.001†
Social allowance, %	10.6 ± 0.4	13.5 ± 1.0	0.002†
Low household income, %	48.5 ± 0.7	50.4 ± 1.4	0.200†
Food insecurity	2.0 ± 0.2	2.2 ± 0.4	0.626†
Live alone, %	15.8 ± 0.4	19.0 ± 1.0	0.001†
Condition, %			
Hypertension	62.3 ± 0.6	65.3 ± 1.3	0.034†
Arthritis	30.3 ± 0.5	35.4 ± 1.4	<0.001†

DM	22.5 ± 0.5	30.7 ± 1.4	<0.001†
CVD	5.6 ± 0.3	8.9 ± 0.8	<0.001†
Asthma	5.6 ± 0.3	5.1 ± 0.6	0.406†
Pulmonary tuberculosis	0.2 ± 0.1	0.2 ± 0.1	0.578†
Stroke	4.0 ± 0.2	6.1 ± 0.7	<0.001†
Cancer, current	1.9 ± 0.2	4.4 ± 0.6	<0.001†
Hepatitis B	1.3 ± 0.1	0.9 ± 0.2	0.156†
Hepatitis C	0.3 ± 0.0	0.2 ± 0.1	0.669†
Liver cirrhosis	0.6 ± 0.1	0.7 ± 0.2	0.701†
CRF	14.2 ± 0.5	34.0 ± 1.2	<0.001†

Values are expressed as either percentage ± standard error (SE) of the percentage or mean ± SE.

Abbreviations: *Hb* hemoglobin, *BMI* body mass index, *DM* Diabetes mellitus, *CVD* Cardiovascular disease, *CRF* Chronic renal failure

*P-values were derived from the independent t-test.

†P-values were derived from the chi-squared test.

Table 2. Analysis of Risk Factors for Anemia in Older Adults

	Univariate Analysis		Multivariate Analysis	
Variable	**OR (95% CI)**	***P*-Value**	**OR (95% CI)**	***P*-Value**
Mean age, years	1.077 (1.066-1.088)	<0.001	1.057 (1.045-1.070)	<0.001
Women, %	1.318 (1.167-1.488)	<0.001	1.270 (1.097-1.471)	0.001
Mean Hb level	0.022 (0.018-0.027)	<0.001		
Underweight (BMI < 18), %	2.322 (1.717-3.139)	<0.001	2.263 (1.622-3.157)	<0.001
Social allowance, %	1.311 (1.107-1.552)	0.002	1.179 (0.971-1.431)	0.097
Low household income, %	1.077 (0.961-1.206)	0.201		
Food insecurity	1.104 (0.742-1.644)	0.626		
Live alone, %	1.247 (1.093-1.423)	0.001	1.044 (0.890-1.225)	0.599
Condition, %				
Hypertension	1.139 (1.010-1.284)	0.034	0.887 (0.777-1.012)	0.075
Arthritis	1.263 (1.114-1.432)	<0.001	1.174 (1.017-1.354)	0.028
DM	1.525 (1.330-1.748)	<0.001	1.419 (1.229-1.638)	<0.001
CVD	1.637 (1.323-2.025)	<0.001	1.396 (1.123-1.737)	0.003

Asthma	0.896 (0.692-1.160)	0.406		
Pulmonary tuberculosis	0.659 (0.149-2.903)	0.581		
Stroke	1.552 (1.213-1.987)	<0.001	1.344 (1.020-1.772)	0.036
Cancer, current	2.360 (1.689-3.298)	<0.001	2.738 (1.937-3.870)	<0.001
Hepatitis B	0.670 (0.384-1.169)	0.158		
Hepatitis C	0.787 (0.262-2.369)	0.670		
Liver cirrhosis	1.139 (0.585-2.216)	0.702		
CRF	3.107 (2.734-3.531)	<0.001	2.513 (2.174-2.904)	<0.001

Abbreviations: *OR* odds ratio, *CI* confidence interval, *Hb* hemoglobin, *BMI* body mass index, *DM* diabetes mellitus, *CVD* cardiovascular disease, *CRF* chronic renal failure.

Table 3. Analysis of the Etiologies of Anemia in Older Adults Using the 2010-2012 KNHANES Data

Variable	Population Aged <65 Years With Anemia (n = 2,344,583.143)	Older Adults With Anemia (n = 663,378.269)	*P*-Value
IDA	49.7 ± 2.1	9.9 ± 1.6	<0.001
Underweight	5.3 ± 0.9	5.4 ± 1.5	0.989*
Cancer	0.8 ± 0.3	2.3 ± 0.7	0.026*
DM	5.7 ± 0.9	27.7 ± 2.7	<0.001*
Hypertension	13.6 ± 1.2	69.0 ± 2.6	<0.001*
CRF	3.2 ± 0.6	30.8 ± 2.4	<0.001*
Stroke	0.7 ± 0.3	5.5 ± 1.3	<0.001*
CVD	0.8 ± 0.3	8.9 ± 1.6	<0.001*
Arthritis	6.2 ± 0.9	33.7 ± 2.9	<0.001*

Values are expressed as percentage ± standard error.

**P*-values were derived from the chi-squared test.

Abbreviations: *KNHANES* Korea National Health and Nutrition Examination Survey, *IDA* iron-deficiency anemia, *DM* Diabetes mellitus, *CRF* Chronic renal failure, *CVD* Cardiovascular disease.

FIGURE LEGENDS

Figure 1. Flow chart of the study sample. Data from the 2007-2016 Korea National Health and Nutrition Examination Survey (KNHANES).

Figure 2. Prevalence of anemia according to age group.

Figures

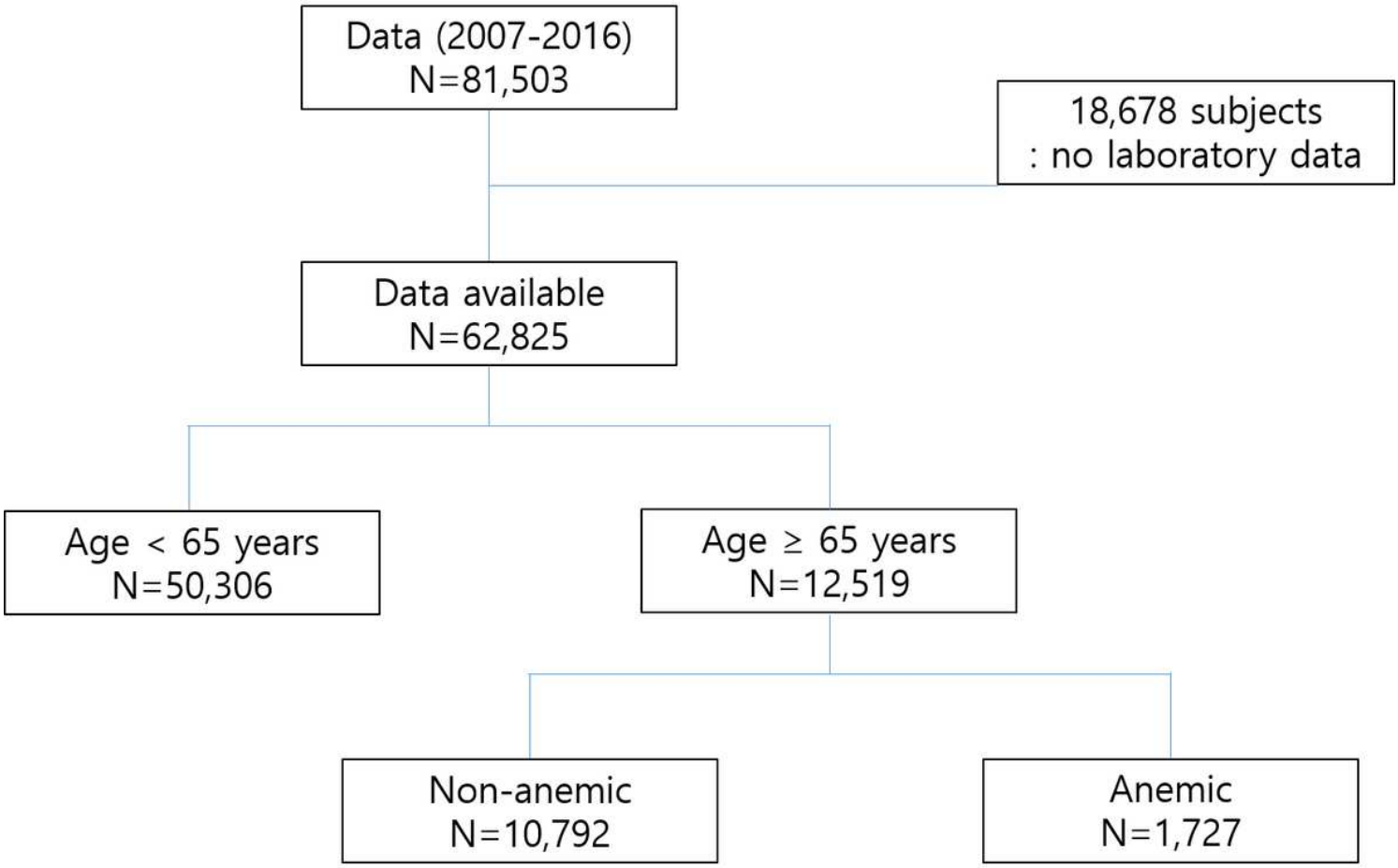

Figure 1

Flow chart of the study sample. Data from the 2007-2016 Korea National Health and Nutrition Examination Survey (KNHANES).

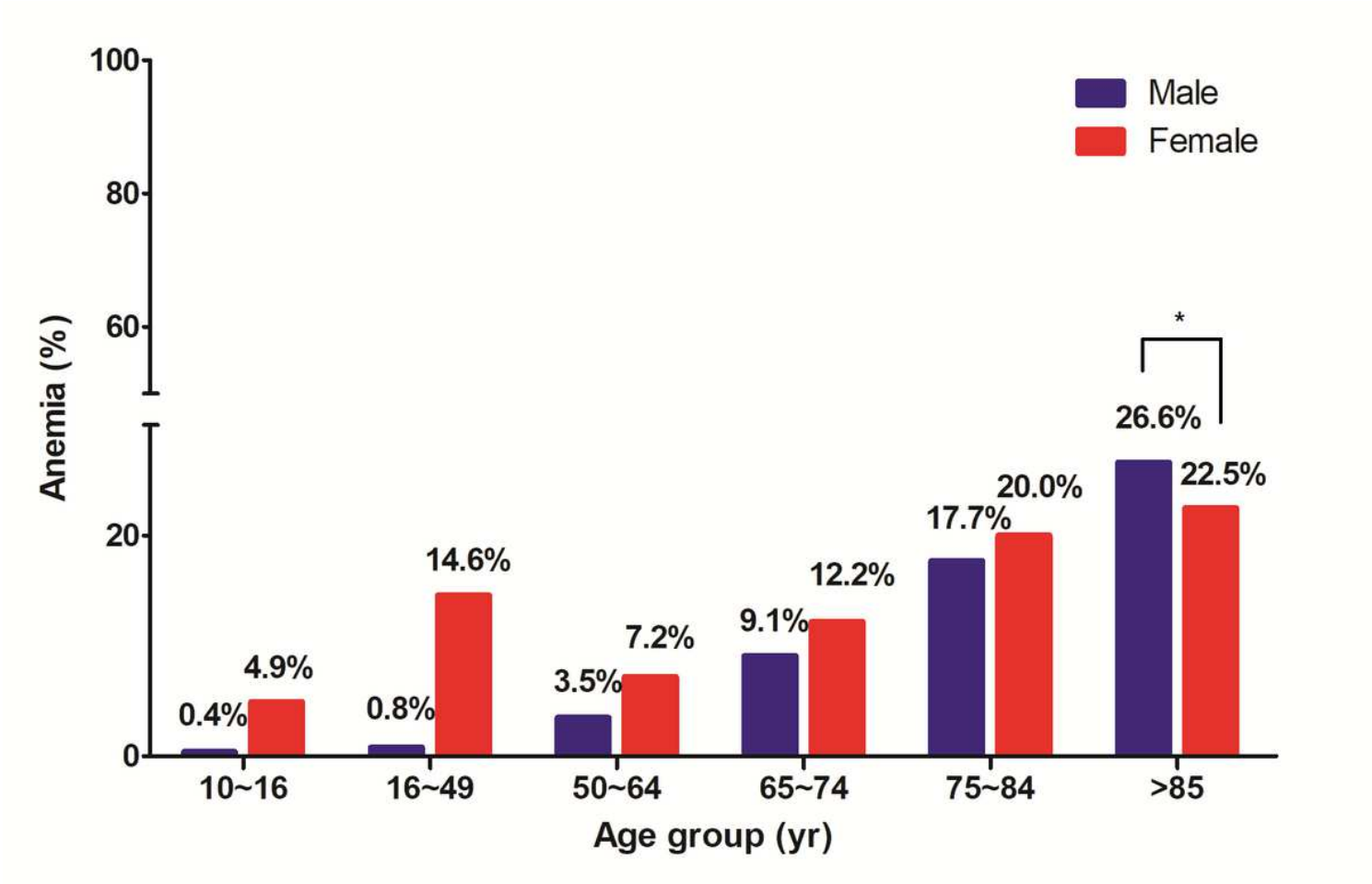

Figure 2

Prevalence of anemia according to age group.