Cross-sectional and longitudinal association between hemoglobin concentrations and hypertension incidence: a population-based cohort study

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Cross-sectional and longitudinal association between hemoglobin concentrations and hypertension incidence: a population-based cohort study

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ABSTRACT

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Objective: To investigate cross-sectional and longitudinal associations between hemoglobin concentration and hypertension in a Korean community population.

Methods: Between 2006 and 2013, this study examined 4,899 participants with a mean age of 56.6 (35-88) years in a rural community. After excluding 298 participants with a history of myocardial infarction or stroke and 215 participants with abnormally low hemoglobin levels (men <13 g/dL and women <11 g/dL), this cross-sectional analysis was performed on 1,684 men and 2,809 women. Longitudinal associations were evaluated in 675 men and 1,119 women, after excluding 2,699 participants with hypertension at baseline and those who did not participate in follow-up examinations. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of antihypertensive treatment at baseline and follow-up.

Results: The mean hemoglobin level was significantly higher in people with hypertension than in those without hypertension (p = 0.003 for men, p = 0.015 for women). Cross-sectional analysis of participants aged under 60 years old revealed an odds ratio (OR) (95% confidence interval [CI]) for hypertension of 1.16 (0.96-1.40) per one standard deviation (SD) increase in hemoglobin concentration (1.2 g/dL) in men after adjusting for age, body mass index, lifestyle factors, comorbidities, serum blood urea nitrogen, and serum creatinine levels. However, the OR (95% CI) for hypertension per one standard deviation (SD) increase in hemoglobin concentration (1.2 g/dL) was

1.28 (1.09-1.50) in women after adjusting for age, body mass index, lifestyle factors, comorbidities, serum blood urea nitrogen, and serum creatinine. In participants over 60 years of age, men (OR1.15, 95% CI 0.93-1.42) and women (OR 0.94, 95% CI 0.78-1.13) had non-significant association with hypertension.

In longitudinal analysis for participants aged under 60 years of age, the relative risks (95% CI) for incident hypertension per one SD increase in hemoglobin concentration were 0.96 (0.85 - 1.09) in men and 1.00 (0.91 - 1.10) in women after adjusting for age, body mass index, lifestyle factors, serum blood urea nitrogen, serum creatinine, baseline comorbidities, and baseline blood pressure. In participants aged above 60 years of age, the relative risks (95% CI) for incident hypertension per one SD increase in hemoglobin concentration were 1.01 (0.86 - 1.19) in men and 1.01 (0.85 - 1.19) in women after adjusting for age, body mass index, lifestyle factors, serum blood urea nitrogen, serum creatinine, baseline comorbidities, and baseline blood pressure.

Conclusion: The results of this study revealed significant associations between higher hemoglobin concentrations and the prevalence of hypertension and blood pressure among participants less than 60 years of age. However, there was no significant association between higher hemoglobin

concentrations and incident hypertension after adjusting for age, body mass index, lifestyles, serum blood urea nitrogen, serum creatinine, diabetes, hypercholesterolemia, and systolic blood pressure, regardless of age.

Keywords: Hemoglobin, Hypertension, Cohort study, Korean population

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Ⅰ. INTRODUCTION

1. *Background*

Hemoglobin is the red blood cell protein responsible for oxygen transportation and delivery (Anthea et al., 1993). It is also involved in the

transport of other gases, including carbon dioxide (CO2) and nitric oxide (NO) (Epstein and Hsia, 1998; Patton, 2015), which are a critical regulators of vascular homeostasis (Ignarro et al., 1987; Palmer, Ashton and Moncada, 1988; Palmer, Ferrige and Moncada, 1987). In addition to maintaining basal vasodilator tone, NO inhibits smooth muscle proliferation and has antioxidant and anti-inflammatory activity (Gladwin, Crawford and Patel, 2004).

The normal ranges of hemoglobin levels in men and women are 13.3–18.0 and 11.6–16.0 g/dL, respectively (Woo, Kim and Park, 2008). Concentrations below normal levels indicate anemia, which is characterized by a decreased quantity of red blood cells, often accompanied by diminished hemoglobin levels or altered red blood cell morphology (Kassebaum et al., 2014). Anemia, especially when severe, can be a risk factor for infection (Dunne et al., 2002), cardiovascular disease (CVD) outcomes, and all-cause mortality (Al-Ahmad et al., 2001; Elhendy et al., 2003; Jurkovitz et al., 2003; Sabatine et al., 2005; Vlagopoulos et al., 2005). Anemia is also associated with decreased cognitive performance and dementia (Sachdev, Gera and Nestel, 2005; Tamura et al., 2016).

However, recent studies have reported both anemia and high-normal hemoglobin levels are associated with adverse outcomes. In older individuals

without dementia, both lower and higher hemoglobin levels are associated with an increased hazard for developing Alzheimer disease and more rapid cognitive decline (Shah et al., 2011). The Prevention of REnal and Vascular ENd-stage Disease (PREVEND) study reported that both severe anemia and high-normal hemoglobin concentrations are associated with increased incidence of heart failure (Klip et al., 2015). Many cross-sectional studies have observed an association between high hemoglobin levels and hypertension or high blood pressure (Atsma et al., 2012; Lee, Rim and Kim, 2015; Rasmussen et al., 2015; Ren et al., 2014; Shimizu et al., 2014b). A Japanese study reported slightly low hemoglobin levels to be positively associated with arterial stiffness, which is closely related to hypertension, in community-dwelling women (Kawamoto et al., 2012). In addition, administration of erythropoietin, an erythropoiesis-stimulating protein used for treatment of anemia, was related to elevated blood pressure among hemo-dialysis patients (Kanbay et al., 2007).

The results of previous studies indicate that high hemoglobin concentrations can cause vasoconstriction and consequent increases in blood pressure due to reduce NO availability for vascular smooth muscle cells (Cabrales et al., 2011; Cabrales et al., 2009). However, other studies have reported that mean arterial blood pressure is not correlated with blood

viscosity in healthy populations because of intact vasodilation function (Vázquez, 2012).

Cardiovascular disease (CVD) is the leading cause of death worldwide. The World Health Organization (WHO) has reported that an estimated 17.5 million people died from CVD in 2012, representing 31% of all global deaths (WHO, 2014). Hypertension is a risk factor for CVD. (Lawes, Vander Hoorn and Rodgers, 2008; Rasmussen et al.). Worldwide, about 54% and 47% of cases of stroke and ischemic heart disease, respectively, were attributable to high blood pressure (Lawes, Vander Hoorn and Rodgers, 2008). Therefore, maintaining blood pressure at appropriate levels and decreasing risk factors are key for CVD prevention. It is also imperative to increase our knowledge about the factors associated with blood pressure.

Previous studies have reported increased hemoglobin levels to be associated with CVD risk factors such as high blood pressure (Atsma et al., 2012; Lee, Rim and Kim, 2015; Rasmussen et al., 2015; Ren et al., 2014; Shimizu et al., 2014b) and arterial stiffness (Kawamoto et al., 2012) in healthy individuals.

Although cross-sectional studies have thoroughly investigated the relationship between hemoglobin and hypertension in diverse populations (Atsma et al., 2012; Lee, Rim and Kim, 2015; Rasmussen et al., 2015; Ren et

al., 2014; Shimizu et al., 2014a), researches have yet to assess the impact of hemoglobin concentration on incident hypertension via longitudinal analyses.

2. Objectives

The current study assessed the association between hemoglobin concentration and incident hypertension.

Specifically, the goals of this study were to:

(1) assess the cross-sectional relationship between hemoglobin concentration and hypertension; and

(2) evaluate the longitudinal association between hemoglobin concentration and incident hypertension

Ⅱ. METHODS

1. Study population

This study used data from the Korean Genome and Epidemiology Study (KoGES)-Kangwha study, an ongoing community-based prospective cohort study. Over the course of 10 years, the study has recruited and examined approximately 5,000 participants aged 35 to 88 years living on Kangwha Island, through questionnaires, physical examinations, and blood tests. Between 2006 and 2011, 4,899 individuals underwent the baseline survey. After the baseline health examinations, cohort members were invited to undergo follow-up health examinations every three to five years.
The current study analyzed baseline and follow-up data collected between 2006 and 2013, with follow-up data ranging from 1 to 8 years (mean 4.4 years).

This cross-sectional analysis was performed on data from 4,493 individuals after excluding those with a history of myocardial infarction (n = 125) or cerebrovascular accident (n = 173), as well as those with abnormally low hemoglobin concentrations (n = 215, <13 g/dL for men and <11 g/dL for

women).

After additionally excluding 1,159 individuals who did not participate in follow-up examinations and 1,540 with hypertension at baseline, longitudinal analysis was performed on data from a total of 1,794 individuals (Figure 1). All participants provided written informed consent. The study protocol was approved by the Institutional Review Board of Yonsei University Health system and monitored by the Human Research Protection Center of Severance Hospital, Yonsei University Health System (2-1040939-AB-N-01-2016-105).

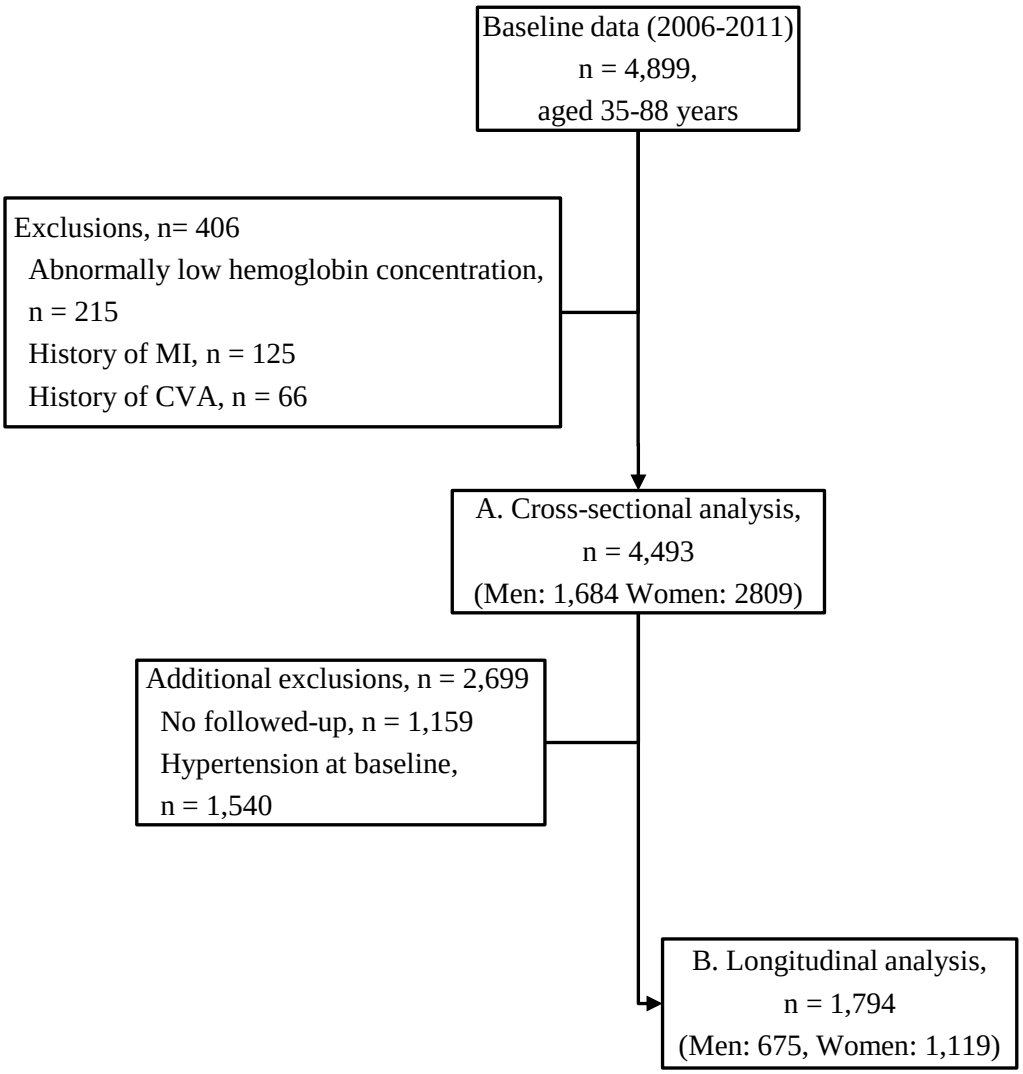


Figure 1. Flowchart of the selection criteria for the final study population
MI: myocardial infarction; CVA: cerebrovascular accident

2. Measurements

A. Questionnaires

All participants were interviewed individually using a standardized questionnaire to obtain information about socio-demographic characteristics, personal medical history, alcohol intake, cigarette smoking, and physical activity. Trained interviewers conducted face-to-face interviews according to a predefined protocol and double-checked for appropriate responses. Personal histories of hypertension, diabetes mellitus, hypercholesterolemia, myocardial infarction, cerebrovascular accident, and other diseases were obtained. Participants were asked if they had continually taken medicine for at least three months; the name of medicine and the duration of taking the medicine were also recorded. Alcohol intake was categorized into current drinking and former/non-drinking. Participants were asked whether they had ever consumed alcoholic beverages in their lifetimes. Those who reported consuming at least one drink of any alcoholic beverage every month were considered current alcohol drinkers. Participants who had stopped or never drunk were considered former/non-drinkers (Baik and Shin, 2008).

Current smokers were defined as those who had smoked more than 100 cigarettes in their lifetimes and reported presently smoking. Former smokers

were those who had smoked more than 100 cigarettes in their lifetimes but had not smoked recently, and never smokers were those individuals who reported smoking fewer than 100 cigarettes. Smoking status was assessed based on responses to a self-reported questionnaire, and individuals were classified into former/non-smoking and current cigarette smoking categories. Regular physical activity was assessed by responses to the question; "Do you regularly exercise to sweating?". Based on their answers, individuals were categorized into those who did and did not perform regular physical activity (Lee et al., 2012).

B. Physical examinations

Standing height was measured to the nearest 0.1 cm with an extensometer, and body weight was measured to the nearest 0.1 kg with a digital scale (SECA-200; SECA, Hanburg, Germany). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Resting systolic blood pressure (SBP) and diastolic blood pressure (DBP) were repeatedly measured at five-minute intervals using an automatic oscilloscopic sphygmomanometer (Dinamap 1846 SX/P; GE Healthcare, Waukesha, WI, USA). If the first and second measurements differed by $\geq$10 mmHg, then additional measurements were performed, and the average of

the last two measurements was used for analysis. Hypertension was defined as elevated blood pressure (SBP ≥140 mmHg or DBP ≥90 mmHg) or use of antihypertensive medication.

C. Laboratory tests

Blood samples were collected from the antecubital vein of the participants after at least 8 hours of fasting. The blood samples were analyzed at a central research laboratory for measurements of complete blood counts, total cholesterol, triglyceride, fasting glucose, serum blood urea nitrogen (BUN), and creatinine. Hemoglobin concentrations were measured by the impedance method using an automatic analyzer (ADVIA 120, Bayer Corp, Tarrytown, NY, USA). Diabetes mellitus was defined as elevated fasting blood glucose level (≥126 mg/dL) or glycated hemoglobin (HbA1c; ≥6.5%) levels, or treatment for diabetes. Hypercholesterolemia was defined as elevated total cholesterol (≥230 mg/dL) or triglyceride (≥200 mg/dl) levels, or use of lipid-lowering medication.

3. Statistical analysis

Baseline characteristics were described for a total of 4,493 participants according to sex using Student's t- test and chi-square test. Student's t-test, chi-square test, and Wilcoxon test were used to assess statistical differences in baseline characteristics, including hemoglobin, in relation to the prevalence of hypertension. Analysis of variance (ANOVA) tests were used to determine statistical differences in blood pressure and each covariate at follow-up according to quartiles of baseline hemoglobin concentrations. Baseline hemoglobin concentrations in men and women were divided into four groups, according to quartile. Since the mechanisms for hypertension in elderly individuals differ from those in younger individuals, participants were divided by age (<60 and ≥ 60 years) (Lionakis et al., 2012). Logistic regression analysis was conducted to assess the odds ratios for cross-sectional associations between hemoglobin concentrations and hypertension.

A generalized linear model was used to estimate the relative risks (RRs) for incident hypertension according to baseline hemoglobin concentrations. For these analyses, two models were used: model 1 was adjusted for age, BMI, and study years (only in cross-sectional analysis); and model 2 was adjusted for alcohol intake, smoking status, regular physical activity,

diabetes, hypercholesterolemia, serum BUN, serum creatinine, and baseline SBP (only in longitudinal analysis). Smoking status was not included in analyses involving women because of their very low smoking rate (2.2%).

To obtain additional insights into the linearity of the association between hemoglobin concentration and hypertension, penalized cubic spline was used (Hagstrom et al., 2009). All statistical analyses were performed using SAS, version 9.4.0 (SAS Inc., Cary, NC, USA) and R, version 3.0.3. All analyses were two-sided and p-values less than 0.05 were considered statistically significant.

III. RESULTS

1. Study population characteristics

Table 1 shows the general characteristics at baseline separately for men and women. Men were older, with SBP, DBP, triglyceride levels, fasting glucose levels, BUN, and creatinine levels, but lower BMI and total cholesterol levels than female participants.

Cigarette smoking, alcohol drinking, and regular physical activity were more frequent in men than in women. Hemoglobin concentrations were significantly higher in men than in women (14.9 vs. 13.1 g/dL, respectively; $p < 0.001$). However, the prevalence of hypertension was not significantly different between men and women (34.8% vs. 34.0%, respectively; $p = 0.590$).

Table 1. Baseline characteristics of the study participants

Variables (n = 4493)	Men (n = 1684)	Women (n = 2809)	p value
Age, year	57.2 ± 8.9	56.3 ± 9.0	0.001
Body mass index, kg/m^2	24.4 ± 2.9	24.8 ± 3.2	<.001
Hemoglobin, g/dL	14.9 ± 1.0	13.1 ± 0.9	<.001
Systolic blood pressure, mmHg	121.7 ± 16.6	119.3 ± 18.1	<.001
Diastolic blood pressure, mmHg	77.7 ± 10.0	71.8 ± 10.2	<.001
Total cholesterol, mg/dL	190.0 ± 31.9	200.4 ± 34.8	<.001
Triglyceride, mg/dL	129.0 (92.5-191.0)	120.0 (86.0- 168.0)	<.001*
Fasting glucose, mg/dL	99.3 ± 21.4	95.0 ± 18.3	<.001
Serum blood urea nitrogen, mg/dL	16.4 ± 4.3	15.2 ± 4.3	<.001
Serum creatinine, mg/dL	1.1 ± 0.1	0.9 ± 0.1	<.001
Post menopause		2114 (75.3)	N/A
Current alcohol drinking	1052 (62.5)	749 (26.7)	<.001
Current cigarette smoking	519 (30.8)	64 (2.3)	<.001
Regular physical activity	636 (37.8)	961 (34.2)	0.018
Hypertension	586 (34.8)	954 (34.0)	0.590
Diabetes	250 (14.9)	374 (13.3)	0.164
Hypercholesterolemia	533 (31.7)	961(34.2)	0.084

Data expressed as means ± standard deviation, median (25 to 75%), or numbers (%)

* Wilcoxon rank sum test

2. Differences in baseline characteristics according to the prevalence of hypertension

Table 2 and 3 show the baseline characteristics of the study participants according to the prevalence of hypertension at baseline. Men with hypertension were older, with higher BMI, triglyceride and fasting glucose levels, serum BUN, as well as higher frequencies of current alcohol drinking, diabetes, and hypercholesterolemia, than men without hypertension (Table 2). Mean age, BMI, total cholesterol, triglyceride levels, fasting glucose levels, serum BUN, and creatinine were significantly higher in women with hypertension compared to those without. Post-menopause, diabetes, and hypercholesterolemia were more frequent in women with hypertension, whereas current alcohol drinking was more common in those without (Table 3). Mean baseline hemoglobin concentrations were significantly higher in men and women with hypertension than in those without ($p = 0.003$ for men, $p = 0.015$ for women).

Table 2. Characteristics of men according to prevalence of hypertension at baseline

Men (n = 1684)	Without hypertension (n = 1,098)	Hypertension (n = 586)	p value
Age, year	56.3 ± 8.8	59.0 ± 9.0	<.001
Body mass index, kg/m^2	24.0 ± 2.8	25.1 ± 2.9	<.001
Hemoglobin, g/dL	14.9 ± 1.0	15.0 ± 1.0	0.003
Total cholesterol, mg/dL	190.0 ± 31.8	190.0 ± 31.9	0.975
Triglyceride, mg/dL	124.0 (87.0-180.0)	148.0 (103.0-212.0)	<.001*
Fasting glucose, mg/dL	97.0 ± 18.7	103.6 ± 25.3	<.001
Serum blood urea nitrogen, mg/dL	16.3 ± 4.2	16.6 ± 4.5	0.135
Serum creatinine, mg/dL	1.07 ± 0.1	1.09 ± 0.1	<.001
Current alcohol drinking	654 (59.6)	398 (67.9)	0.001
Current cigarette smoking	361 (32.9)	158 (27.0)	0.015
Regular physical activity	408 (37.2)	228 (39.0)	0.497
Diabetes	126 (11.5)	124 (21.2)	<.001
Hypercholesterolemia	309 (28.1)	224 (38.2)	<.001

Data expressed as means ± standard deviation, median (25 to 75%), or numbers (%)
* Wilcoxon rank sum test

Table 3. Characteristics of women according to prevalence of hypertension at baseline

Women (n = 2,809)	Without hypertension (n = 1,855)	Hypertension (n = 954)	p value
Age, year	54.3 ± 8.5	60.2 ± 8.8	<.001
Body mass index, kg/m^2	24.3 ± 3.1	25.7 ± 3.3	<.001
Hemoglobin, g/dL	13.1 ± 0.8	13.2 ± 0.9	0.015
Total cholesterol, mg/dL	199.5 ± 34.2	202.2 ± 35.8	0.046
Triglyceride, mg/dL	111.0 (81.0-155.0)	138.0 (98.0-193.0)	<.001*
Fasting glucose, mg/dL	93.0 ± 16.9	98.8 ± 20.2	<.001
Serum blood urea nitrogen, mg/dL	14.9 ± 4.2	15.9 ± 4.4	<.001
Serum creatinine, mg/dL	0.87 ± 0.1	0.90 ± 0.1	<.001
Post menopause	1280 (69.1)	834 (87.4)	<.001
Current alcohol drinking	518 (28.0)	231 (24.2)	0.039
Current cigarette smoking	48 (2.6)	16 (1.7)	0.162
Regular physical activity	633 (34.2)	328 (34.4)	0.940
Diabetes	173 (9.3)	201 (21.1)	<.001
Hypercholesterolemia	546 (29.4)	415 (43.5)	<.001

Data expressed as means ± standard deviation, median (25 to 75%), or numbers (%)
* Wilcoxon rank sum test

3. Cross-sectional association between hemoglobin concentration and hypertension

Table 4 outlines the cross-sectional associations between hemoglobin concentrations and hypertension for men and women. In the unadjusted model of participants <60 years of age, the fourth quartile group had significantly higher odds for having hypertension in both men and women (OR 1.71, 95% CI 1.09-1.50 for men; OR 1.99, 95% CI 1.43-2.76 for women). However, after adjusting for age, BMI, study years, lifestyle factors, comorbidities, and serum BUN and creatinine levels, only the relationships in women persisted with statistically significant ORs of 1.62 (95% CI 1.14 – 2.31). Among those aged ≥ 60 years, the fourth quartile group showed a significantly higher OR of 1.58 (95% CI, 1.02-2.45) in men, compared to the first quartile. After adjusting for age, BMI, lifestyle factors, comorbidities, and serum BUN and creatinine levels, this association disappeared in men. A significant relationship between one SD increase in hemoglobin and the prevalence of hypertension was only observed for women aged under 60 years of age.

Table 4. Cross-sectional association between hemoglobin concentration and hypertension at baseline

Baseline hemoglobin, g/dL	No. of total	No. of hypertension (%)	Odds ratio (95% confidence interval) Unadjusted model	Model 1*	Model 2†
Age < 60 years					
Men					
<14.1	142	34 (23.9)	1.00	1.00	1.00
14.1-<14.8	243	66 (27.2)	1.20 (0.74- 1.94)	1.06 (0.65- 1.73)	1.01 (0.61- 1.67)
14.8-<15.5	284	90 (31.7)	1.51 (0.95- 2.39)	1.36 (0.84- 2.18)	1.29 (0.79- 2.10)
15.5≤	330	114 (34.6)	1.71 (1.09- 2.68)	1.50 (0.94- 2.39)	1.33 (0.82-2.16)
Continuous, per 1 SD	999	304 (30.4)	1.26 (1.06- 1.50)	1.23 (1.02- 1.47)	1.16 (0.96- 1.40)
Women					
<12.4	343	69 (20.1)	1.00	1.00	1.00
12.4-<13.0	430	91 (21.2)	1.06 (0.74-1.51)	0.98 (0.67- 1.41)	0.97 (0.67- 1.42)
13.0-<13.7	556	138 (24.8)	1.33 (0.96-1.85)	1.24 (0.88- 1.74)	1.21 (0.86- 1.72)
13.7≤	478	157 (32.9)	1.99 (1.43-2.76)	1.70 (1.20- 2.41)	1.62 (1.14- 2.31)
Continuous, per 1 SD	1807	455 (25.2)	1.43 (1.23-1.66)	1.32 (1.13- 1.55)	1.28 (1.09- 1.50)
Age ≥ 60 years					
Men					
<14.1	181	66 (36.5)	1.00	1.00	1.00
14.1-<14.8	176	68 (38.6)	1.07 (0.70-1.65)	1.07 (0.68- 1.67)	1.07 (0.68- 1.69)
14.8-<15.5	167	70 (41.9)	1.23 (0.79-1.90)	1.15 (0.73- 1.80)	1.04 (0.65- 1.65)
15.5≤	161	78 (48.5)	1.58 (1.02-2.45)	1.48 (0.93- 2.35)	1.26 (0.77- 2.05)
Continuous, per 1 SD	685	282 (41.2)	1.29 (1.06-1.56)	1.23 (1.01- 1.51)	1.15 (0.93- 1.42)
Women					
<12.4	234	129 (55.1)	1.00	1.00	1.00
12.4-<13.0	229	106 (46.3)	0.72 (0.50- 1.05)	0.77 (0.53- 1.12)	0.75 (0.51- 1.10)
13.0-<13.7	284	128 (45.1)	0.65 (0.46- 0.93)	0.69 (0.48- 1.00)	0.69 (0.47- 1.00)
13.7≤	255	136 (53.3)	0.94 (0.65-1.35)	0.96 (0.66- 1.40)	0.92 (0.63- 1.36)
Continuous, per 1 SD	1002	499 (49.8)	0.95 (0.80- 1.13)	0.96 (0.80- 1.15)	0.94 (0.78-1.13)

Hemoglobin 1 SD = 1.2 g/dL; SD: standard deviation

*Model 1: adjusted for age, body mass index, study year

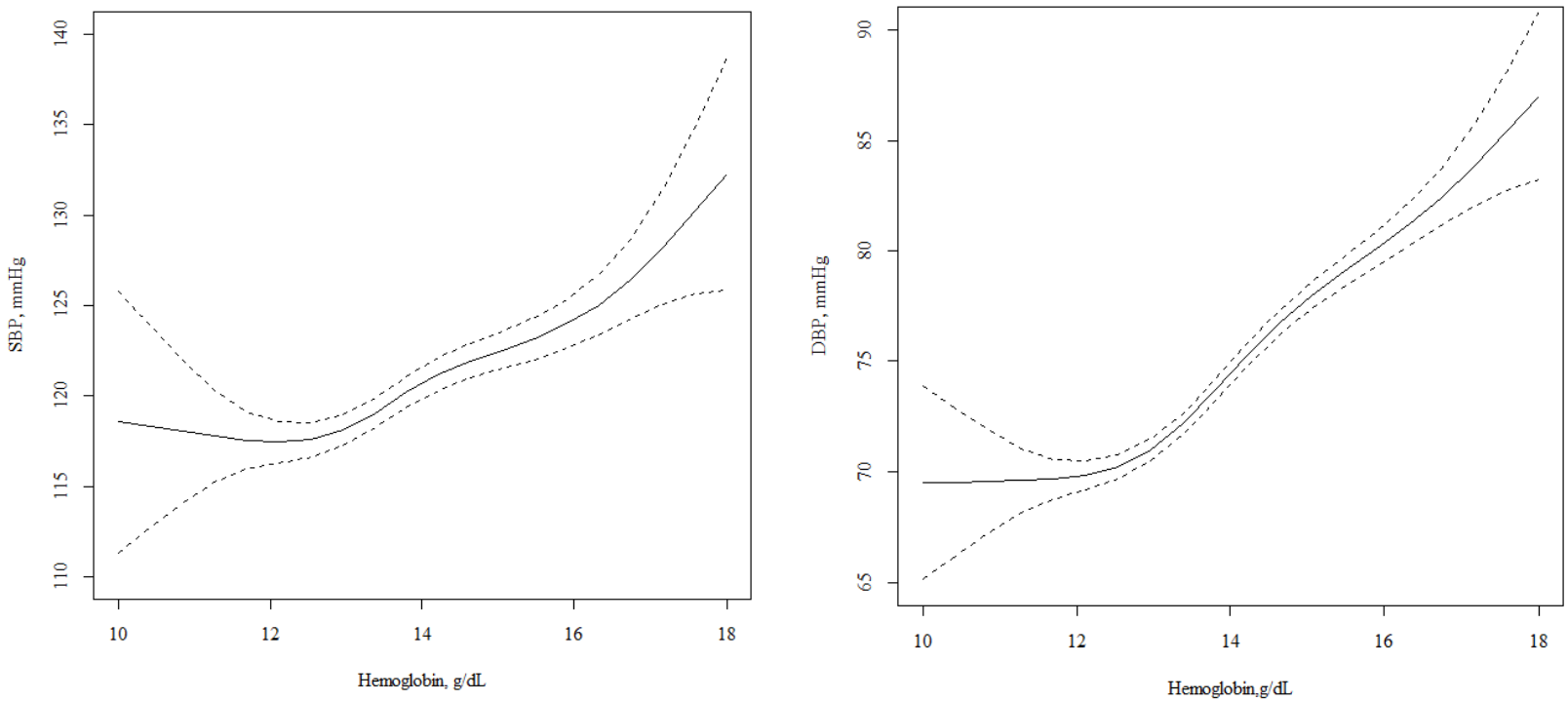
†Model 2: adjusted for age, body mass index, study year, alcohol intake, smoking status (only men), regular physical activity, diabetes, hypercholesterolemia, serum blood urea nitrogen, and serum creatinine

4. Cross-sectional association between hemoglobin concentration and blood pressure

Figure 2 shows that hemoglobin concentration as a continuous value was linearly associated with blood pressure. However, dividing the participants according to age (<60 and ≥ 60) significantly higher SBP and DBP in the fourth quartile than in the lowest quartile of hemoglobin, in both men and women (Figures 3 and 4).

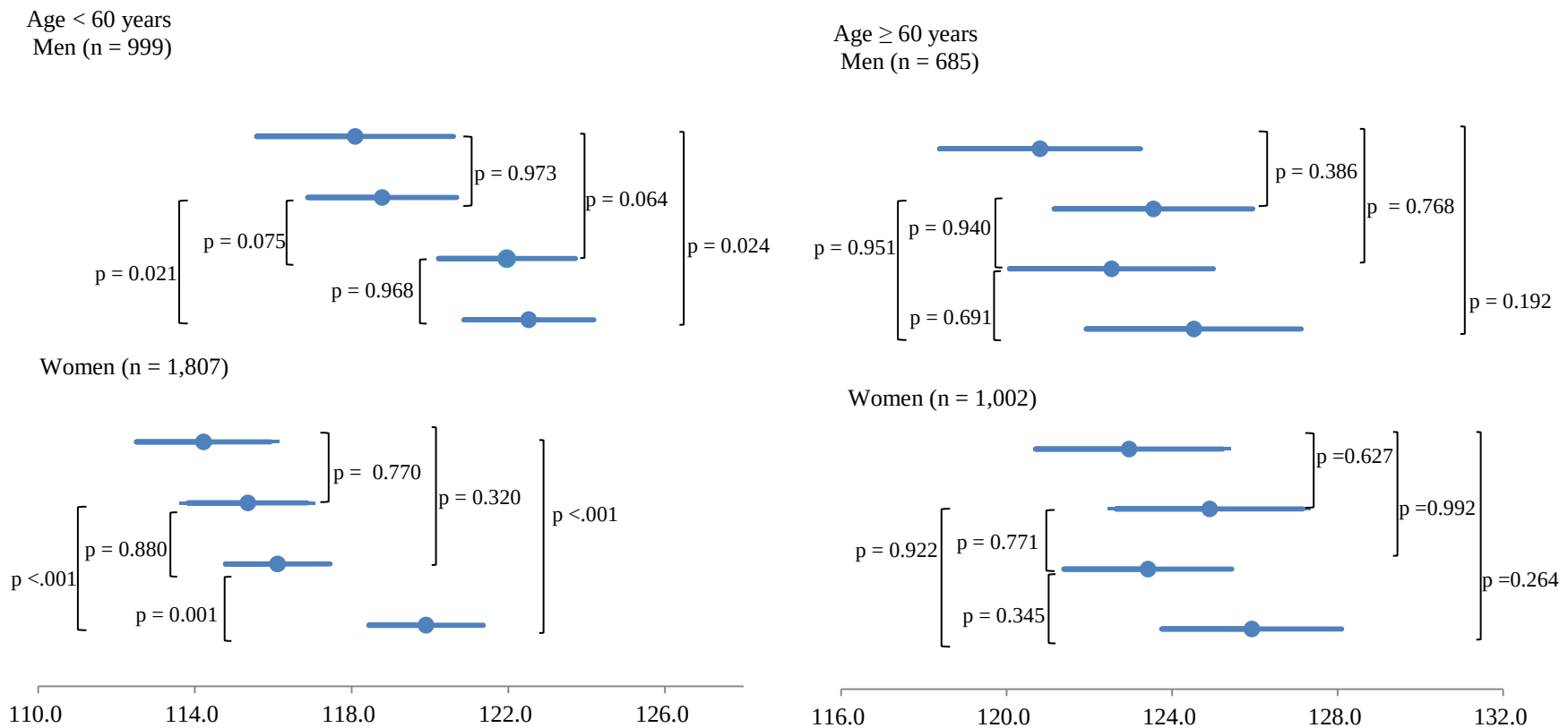
Even after excluding individuals with hypertension, hemoglobin concentration was positively associated with SBP and DBP among those aged <60 years. However, different results were observed among those aged over 60 years (Tables 5 and 6). In regard to SBP, low hemoglobin concentration was significantly related to increasing SBP in men, whereas no significant association was observed in women. However, with respect to DBP, men with hemoglobin concentrations in the third quartile had higher odds for increasing DBP. In contrast, women in the highest quartile of hemoglobin concentration had significantly higher odds compared to those of women with hemoglobin concentrations in the lowest quartile.

Figure 2. Cross-sectional association between hemoglobin concentration and blood pressure



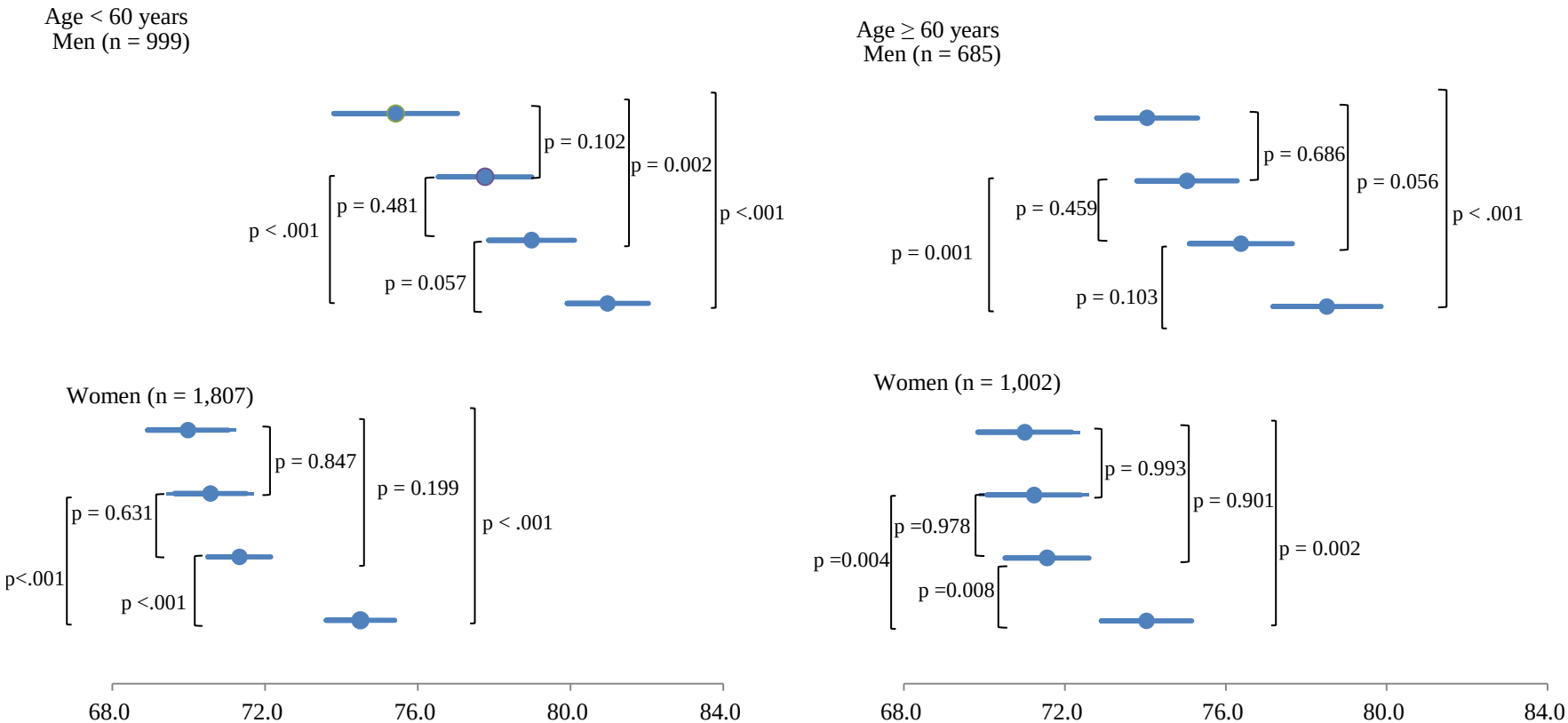
Solid (dotted) lines show odds ratios (95% confidence intervals) for blood pressure in relation to hemoglobin, as a function of penalized regression splines; unadjusted; SBP: systolic blood pressure; DBP: diastolic blood pressure

Figure 3. Mean differences in systolic blood pressure according to quartiles of baseline hemoglobin concentration



Adjusted for age, body mass index, study year, alcohol intake, smoking status (only men), regular physical activity, diabetes, hypercholesterolemia, serum blood urea nitrogen, and serum creatinine levels

Figure 4. Mean differences in diastolic blood pressure according to quartiles of baseline hemoglobin concentration



Adjusted for age, body mass index, study year, alcohol intake, smoking status (only men), regular physical activity, diabetes, hypercholesterolemia, serum blood urea nitrogen, and serum creatinine levels

Table 5. Cross-sectional associations between hemoglobin concentration and systolic blood pressure at baseline after excluding participants with hypertension

Baseline hemoglobin, g/dL	No. of total	Unadjusted model		Model 1*		Model 2†	
		β	p	β	p	β	p
Age < 60 years							
Men							
<14.1	108	Ref		Ref		Ref	
14.1-<14.8	177	3.162	0.022	2.381	0.078	2.361	0.076
14.8-<15.5	194	5.652	<.001	4.536	0.001	4.376	0.001
15.5≤	216	6.331	<.001	4.636	0.001	4.261	0.002
Continuous, per 1 SD	695	2.887	<.001	2.223	<.001	1.987	0.001
Women							
<12.4	274	Ref		Ref		Ref	
12.4-<13.0	339	0.864	0.388	0.023	0.980	-0.123	0.896
13.0-<13.7	418	2.318	0.015	1.639	0.067	1.490	0.097
13.7≤	321	5.800	<.001	4.351	<.001	3.875	<.001
Continuous, per 1 SD	1352	3.101	<.001	2.468	<.001	2.264	<.001
Age ≥ 60 years							
Men							
<14.1	115	Ref		Ref		Ref	
14.1-<14.8	108	4.768	0.006	4.570	0.008	4.946	0.003
14.8-<15.5	97	5.535	0.002	4.801	0.007	4.091	0.020
15.5≤	83	3.571	0.058	3.082	0.103	2.912	0.129
Continuous, per 1 SD	403	2.374	0.005	2.052	0.017	1.947	0.026
Women							
<12.4	105	Ref		Ref		Ref	
12.4-<13.0	123	1.318	0.432	1.734	0.292	1.764	0.284
13.0-<13.7	156	0.730	0.649	1.478	0.355	1.382	0.387
13.7≤	119	1.559	0.361	1.783	0.293	1.431	0.402
Continuous, per 1 SD	503	0.582	0.477	0.629	0.443	0.431	0.603

Hemoglobin 1 SD = 1.2 g/dL; SD: standard deviation

*Model 1: adjusted for age, body mass index, study year

†Model 2: adjusted for age, body mass index, study year, alcohol intake, smoking status (only men), regular physical activity, diabetes, hypercholesterolemia, serum blood urea nitrogen, and serum creatinine

Table 6. Cross-sectional associations between hemoglobin concentration and diastolic blood pressure at baseline after excluding participants with hypertension

Baseline hemoglobin, g/dL	No. of total	Unadjusted model		Model 1*		Model 2†	
		β	p	β	p	β	p
Age < 60 years							
Men							
<14.1	108	Ref		Ref		Ref	
14.1-<14.8	177	3.393	<.001	3.162	0.001	3.045	0.001
14.8-<15.5	194	3.811	<.001	3.504	<.001	3.191	0.001
15.5≤	216	5.942	<.001	5.495	<.001	5.158	<.001
Continuous, per 1 SD	695	2.499	<.001	2.361	<.001	2.175	<.001
Women							
<12.4	274	Ref		Ref		Ref	
12.4-<13.0	339	0.671	0.342	0.331	0.632	0.151	0.826
13.0-<13.7	418	1.272	0.060	0.986	0.136	0.804	0.222
13.7≤	321	4.267	<.001	3.641	<.001	3.096	<.001
Continuous, per 1 SD	1352	2.366	<.001	2.095	<.001	1.852	<.001
Age ≥ 60							
Men							
<14.1	115	Ref		Ref		Ref	
14.1-<14.8	108	1.890	0.058	1.558	0.115	1.781	0.067
14.8-<15.5	97	4.190	<.001	3.529	0.001	3.238	0.002
15.5≤	83	3.145	0.004	2.408	0.028	2.307	0.038
Continuous, per 1 SD	403	2.052	<.001	1.681	0.001	1.619	0.001
Women							
<12.4	105	Ref		Ref		Ref	
12.4-<13.0	123	1.043	0.325	0.729	0.488	0.877	0.399
13.0-<13.7	156	2.078	0.040	1.561	0.126	1.522	0.132
13.7≤	119	3.331	0.002	2.622	0.016	2.357	0.029
Continuous, per 1 SD	503	1.815	<.001	1.419	0.007	1.222	0.019

Hemoglobin 1 SD = 1.2 g/dL; SD: standard deviation

*Model 1: adjusted for age, body mass index, study year

†Model 2: adjusted for age, body mass index, study year, alcohol intake, smoking status (only men), regular physical activity, diabetes, hypercholesterolemia, serum blood urea nitrogen, and serum creatinine

5. Follow-up characteristics according to baseline hemoglobin quartiles

Table 7 and 8 show the follow-up characteristics of men and women according to baseline hemoglobin quartiles. In men, BMI, SBP, DBP, total cholesterol, triglyceride, fasting glucose, and serum creatinine levels significantly increased with increasing to baseline hemoglobin level quartiles (Table 7). However, the incidence of hypertension was not significantly elevated with increasing baseline hemoglobin concentrations. In women, BMI, SBP, DBP, total cholesterol, triglyceride, and fasting glucose levels increased significantly according to increasing baseline hemoglobin quartile concentration (Table 8). The incidence of hypertension in the fourth quartile of hemoglobin was highest (19.5%), and the trend with increasing baseline hemoglobin concentrations was significant ($p < 0.028$).

Table 7. Follow-up characteristics according to baseline hemoglobin quartiles in men

Men (n = 675)	Hemoglobin categories (g/dL)				
	<14.1, n = 182	14.1 - < 14.8, n = 175	14.8 - < 15.5, n = 158	15.5≤, n = 160	p trend
Age, years	63.4 ± 8.0	59.8 ± 8.1	60.8 ± 8.3	58.2 ± 8.9	<.001
Body mass index, kg/m^2	23.3 ± 2.7	24.3 ± 2.6	24.5 ± 2.9	25.1 ± 2.5	<.001
Systolic blood pressure, mmHg	113.1 ± 14.0	117.1 ± 13.7	114.3 ± 13.4	118.8 ± 12.0	0.002
Diastolic blood pressure, mmHg	69.7 ± 9.2	74.3 ± 8.6	73.4 ± 9.4	76.4 ± 7.6	<.001
Total cholesterol, mg/dL	182.7 ± 33.0	187.7 ± 34.4	190.8 ± 31.7	191.5 ± 32.0	0.011
Triglyceride, mg/dL	109.0 (79.0- 157.0)	122.0 (92.0- 165.0)	128.0 (93.0- 174.0)	153.0 (110.0- 212.0)	<.001*
Fasting glucose, mg/dL	94.0 ± 20.2	97.2 ± 24.1	95.3 ± 22.7	100.5 ± 24.9	0.028
Serum blood urea nitrogen, mg/dL	17.5 ± 4.7	16.3 ± 4.2	16.4 ± 4.5	15.9 ± 3.9	0.003
Serum creatinine, mg/dL	1.05 ± 0.1	1.05 ± 0.1	1.06 ± 0.2	1.07 ± 0.1	0.032
Diabetes	20 (11.0)	27 (15.4)	22 (13.9)	32 (20.0)	0.037
Hypercholesterolemia	45 (24.7)	53 (30.3)	50 (31.7)	66 (41.3)	<0.001
Incident hypertension	26 (14.3)	30 (17.1)	28 (17.7)	24 (15.0)	0.805

Data expressed as means ± standard deviation, median (25 to 75%), or numbers (%)

* Wilcoxon rank sum test

Table 8. Follow-up characteristics according to baseline hemoglobin quartiles in women

Women (n = 1,119)	Hemoglobin categories (g/dL)				
	<12.4, n = 323	12.4 - < 13.0, n = 250	13.0 - < 13.7, n = 299	13.7≤, n = 247	p trend
Age, year	58.1 ± 8.2	58.1 ± 7.7	58.0 ± 8.1	57.7 ± 7.6	0.545
Body mass index, kg/m^2	24.1 ± 3.4	24.3 ± 3.0	24.4 ± 3.0	24.9 ± 3.4	0.004
Systolic blood pressure, mmHg	110.3 ± 13.8	113.5 ± 13.2	112.7 ± 13.6	115.7 ± 13.5	<.001
Diastolic blood pressure, mmHg	66.7 ± 8.9	68.1 ± 9.3	68.4 ± 9.2	70.9 ± 8.9	<.001
Total cholesterol, mg/ dL	197.1 ± 35.9	195.5 ± 33.2	197.7 ± 34.0	202.8 ± 38.1	0.049
Triglyceride, mg/dL	108.0 (81.0- 148.0)	119.0 (88.0- 151.5)	105.0 (82.0- 145.0)	125.5 (93.0- 173.0)	0.002*
Fasting glucose, mg/ dL	89.6 ± 11.1	93.5 ± 18.6	91.7 ± 13.1	95.3 ± 21.3	0.001
Serum blood urea nitrogen, mg/dL	15.4 ± 4.0	15.3 ± 4.2	15.5 ± 3.8	15.3 ± 4.6	0.734
Serum creatinine, mg/dL	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.725
Postmenopausal status	255 (79.0)	198 (79.2)	216 (72.2)	195 (79.3)	0.498
Diabetes	31 (9.6)	27 (10.8)	21 (7.0)	42 (17.1)	0.002
Hypercholesterolemia	100 (31.0)	82 (32.8)	105 (35.1)	97 (39.4)	0.032
Incident hypertension	37 (11.5)	33 (13.2)	32 (10.7)	48 (19.5)	0.028

Data expressed as means ± standard deviation, median (25 to 75%), or numbers (%)

* Wilcoxon rank sum test

6. Longitudinal association between baseline hemoglobin concentration and incident hypertension

The relative risk (RR) of incident hypertension at follow-up according to baseline hemoglobin levels for men and women are shown in Table 9. Among participants aged < 60 years, the RR of the fourth quartile group was 0.78 (95% CI 0.41-1.52) in men. Covariate adjustment did not significantly change the null association (RR 0.92, 95% CI 0.70-1.22).

For women, the fourth quartile group exhibited a higher RR than the first quartile group (RR 1.93, 95% CI 1.19-3.12). However, the association was non-significant after adjusting for age, BMI, lifestyle factors, baseline health status, and baseline SBP (RR 1.01, 95% CI 0.84-1.21).

Among those aged ≥ 60 years, the RRs of the fourth quartile group were 1.69 (95% CI 0.76-3.78) in men and 1.29 (95% CI 0.64-2.61) in women. After covariate adjustment, the associations did not significantly change. When assessing the relationship between continuous hemoglobin concentration and incident hypertension, no significant linear relationships were observed in men, women, and all participants (Figure 5).

Table 9. Relative risk of incident hypertension at follow-up according to baseline hemoglobin concentration

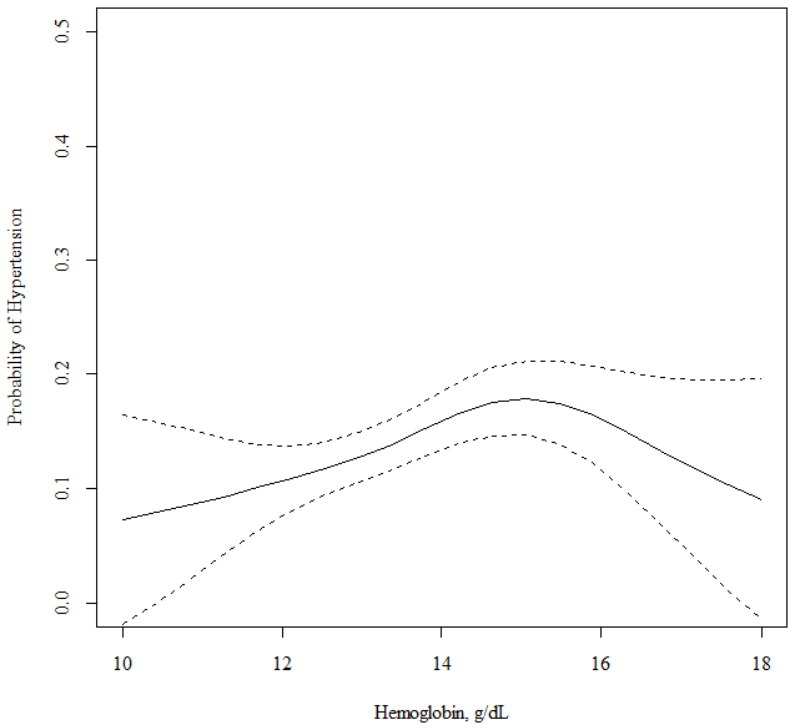
Baseline hemoglobin, g/dL	No. of total	No. of Hypertension (%)	Relative risk (95% confidence interval)		
			Unadjusted model	Model 1*	Model 2†
Age < 60 years					
Men					
<14.1	91	15 (16.5)	1.00	1.00	1.00
14.1-<14.8	123	19 (15.5)	0.94 (0.50- 1.74)	0.96 (0.52- 1.78)	0.97 (0.75- 1.25)
14.8-<15.5	102	17 (16.7)	1.01 (0.54- 1.91)	1.02 (0.54- 1.93)	0.97 (0.74- 1.26)
15.5≤	116	15 (12.9)	0.78 (0.41- 1.52)	0.82 (0.42- 1.61)	0.92 (0.70- 1.22)
Continuous, per 1 SD	432	66 (15.3)	0.92 (0.70- 1.22)	0.95 (0.71- 1.27)	0.96 (0.85- 1.09)
Women					
<12.4	246	24 (9.8)	1.00	1.00	1.00
12.4-<13.0	190	22 (11.6)	1.19 (0.69- 2.05)	1.20 (0.70- 2.05)	1.00 (0.83- 1.19)
13.0-<13.7	222	20 (9.0)	0.92 (0.52- 1.62)	0.89 (0.51- 1.54)	0.97 (0.81- 1.15)
13.7≤	191	36 (18.9)	1.93 (1.19- 3.12)	1.62 (1.01- 2.60)	1.01 (0.84- 1.21)
Continuous, per 1 SD	849	102 (12.0)	1.43 (1.11- 1.83)	1.30 (1.01- 1.66)	1.00 (0.91- 1.10)
Age ≥ 60 years					
Men					
<14.1	91	11 (12.1)	1.00	1.00	1.00
14.1-<14.8	52	11 (21.2)	1.75 (0.82- 3.75)	1.54 (0.73- 3.26)	1.03 (0.74- 1.43)
14.8-<15.5	56	11 (19.6)	1.63 (0.75- 3.50)	1.36 (0.64- 2.89)	1.02 (0.74- 1.41)
15.5≤	44	9 (20.5)	1.69 (0.76- 3.78)	1.24 (0.54- 2.86)	1.03 (0.72- 1.48)
Continuous, per 1 SD	243	42 (17.3)	1.26 (0.90- 1.75)	1.09 (0.76- 1.55)	1.01 (0.86- 1.19)
Women					
<12.4	77	13 (16.9)	1.00	1.00	1.00
12.4-<13.0	60	11 (18.3)	1.09 (0.52- 2.25)	1.30 (0.63- 2.71)	1.01 (0.73- 1.38)
13.0-<13.7	77	12 (15.6)	0.92 (0.45- 1.89)	1.08 (0.53- 2.20)	0.99 (0.74- 1.34)
13.7≤	55	12 (21.8)	1.29 (0.64- 2.61)	1.52 (0.76- 3.04)	1.04 (0.75- 1.45)
Continuous, per 1 SD	269	48 (17.8)	1.01 (0.69- 1.47)	1.10 (0.78- 1.55)	1.01 (0.85- 1.19)

Hemoglobin 1 SD = 1.2 g/dL; SD: standard deviation

*Model 1: adjusted for age and body mass index

†Model 2: adjusted for age, body mass index, alcohol intake, smoking status (only men), regular physical activity, diabetes, hypercholesterolemia, serum blood urea nitrogen, serum creatinine and systolic blood pressure

Figure 5. Longitudinal associations between hemoglobin concentration and incident hypertension



Solid (dotted) lines present relative risk (95% confidence interval) for incident hypertension in relation to hemoglobin, as a function of penalized regression splines; unadjusted

Ⅳ. DISCUSSION

1. Summary of findings

A significant positive association between hemoglobin concentrations and hypertension prevalence was observed in rural Korean women < 60 years of age. However, the association was not significant among those ≥ 60 years of age. After excluding participants with hypertension at baseline, similar results were shown. According to increasing quartiles of baseline hemoglobin concentration, SBP and DBP were significantly higher in men and women. However, there was no significant association between baseline hemoglobin concentration and incident hypertension after adjusting for covariates including baseline SBP. In addition, no differences in mean hemoglobin concentrations were observed based on the effects of antihypertensive drugs, regardless of hypertension control (Appendix).

Regarding the clinical meaning of this study, the population attributable risk (PAR) could be calculated. Men with hemoglobin concentrations below 15.5 g/dL had higher incidence of hypertension (16.3%) than those with hemoglobin concentrations ≥15.5 g/dL (15.0%). However, women with hemoglobin concentrations ≥13.7 g/dL had higher incidence of

hypertension (19%) than those with hemoglobin concentrations < 13.7 g/dL (11.7%). Thus, maintaining hemoglobin concentrations below 13.7 g/dL in women could reduce the incidence of hypertension by 9%, corresponding to a PAR of 9%, if the association between higher hemoglobin concentration and incident hypertension was significant.

2. Comparison with previous studies

Recent cross-sectional studies have reported positive associations between hemoglobin concentration and blood pressure (Atsma et al., 2012; Göbel et al., 1991; Lee, Rim and Kim, 2015; Ren et al., 2014; Shimizu et al., 2014a). A Japanese study demonstrated that higher hemoglobin concentrations were associated with hypertension in non-anemic men and women. After stratifying according to obesity, the association between higher hemoglobin concentration and hypertension was significant only in non-obese participants (BMI <25 kg/m^2) (Shimizu et al., 2014a). A Dutch study of 691,107 voluntary blood donors reported that hemoglobin concentrations were positively associated with SBP and DBP in men and women after adjusting for age, BMI, and mean daily temperature. This study also observed an association between higher hemoglobin concentrations and high blood pressure based on repeated measurement analysis (Atsma et al., 2012).

In a Chinese study, higher hemoglobin concentrations, even within the normal range, were associated with increased prevalence of hypertension and other cardiovascular risk factors, including general obesity, abnormally high lipid profile, increased blood pressure, as well as impaired fasting glucose and high urine acid (Ren et al., 2014) levels. In Kenyan study, hemoglobin concentration was linearly associated with SBP and DBP, after adjusting for

age, sex, total cholesterol, waist circumference, homeostatic model assessment-insulin resistance (HOMA-IR), ethnicity, and smoking status (Rasmussen et al., 2015). Higher hemoglobin levels were positively associated with SBP and DBP in men and women with hemoglobin concentrations ≥8.1 mmol/L (13.0 g/dL) and ≥6.8 mmol/l (11.0 g/dL), respectively, in the general Korean population, using data from Korea National Health and Nutrition Examination Survey (Lee, Rim and Kim, 2015). Because the mechanisms for hypertension vary with age, the current study stratified participants according to age (under 60 years and above 60 years). The results of previous studies were in line with the cross-sectional findings among participants younger than 60 years old in the current study. This result was similar to a recent Chinese study, which reported that the association between increasing quartiles of hematocrit and prehypertension in individuals older than 60 years was not significant, while the association in individuals younger than 60 years was significant (Liu et al., 2015). However, the longitudinal relationship between hemoglobin and incident hypertension has not been fully evaluated in Asian countries.

3. Possible mechanisms

The results of this cross-sectional study showed a significant association between hemoglobin concentration and hypertension, but no longitudinal association between hemoglobin and development of hypertension was observed. These results may suggest that higher hemoglobin concentrations may be related to hypertension, but high hemoglobin concentration itself may not be cause of the hypertension.

Several mechanisms may explain results of the study. First, increased hematocrit and hemoglobin levels can increase blood viscosity, which may elevate blood pressure (Göbel et al., 1991; Lowe et al., 1997). High hemoglobin concentrations can induce vasoconstriction, which may consequently elevate blood pressure due to limited NO availability in vascular smooth muscle cells (Cabrales et al., 2011; Cabrales et al., 2009).

Although this mechanism can explain the cross-sectional results of this study, it does not directly support the hypothesis that increased hemoglobin concentration is a main cause of hypertension. Hypertension is a chronic disease caused by various long-term factors such as a systematic inflammation. Thus, vasoconstriction and high blood pressure may be similar to the symptoms of hypertension, but not the cause.

These findings may suggest that hemoglobin concentration is related to hypertension, because other factors may influence both hemoglobin concentration and hypertension.

Second, the renin-angiotensin-aldosterone system may be related to both hemoglobin concentration and blood pressure. Renin is transformed to angiotensin-2, which causes vasoconstriction. In this process, other tissues may produce angiotensin-2 and stimulate erythropoietin production (Biaggioni et al., 1994; Freudenthaler et al., 1999); (Biaggioni et al., 1994).

Third, endothelial cell damage may increase blood pressure as well as hemoglobin concentration. Endothelial cell damage is associated in increased concentrations of growth factors (Nakamura et al., 1996a) in order to regenerate tissue (Kawaida et al., 1994; Schmidt et al., 1995). Several studies have reported the concentration of serum hepatocyte growth factor concentration is positively associated with hypertension (Nakamura et al., 1998; Nakamura et al., 1996b) as well as increased hemoglobin concentrations (Kadota et al., 2016). Since growth factors enhance hematopoiesis, which produces erythrocytes (Takai et al., 1997), hemoglobin levels may increase with increasing levels of growth factors (Kadota et al., 2016).

4. Limitations and strengths

The present study has several limitations. First, the study population was limited to a single rural area and was not randomly selected. Therefore, these findings may not be generalizable to other populations. Second, the mean follow-up duration was only 4.4 years, which may not have been sufficient time for development of hypertension. Additional experimental and longitudinal studies are needed to further understand this relationship. Third, this study may have introduced measurement errors. Treatment history was measured using a self-reported questionnaire; however, misclassification, if any, would likely be non-differential misclassification bias. Fourth, hemoglobin levels are mainly affected by nutrition and iron metabolism; however, the current study did not control for nutritional effects.

To our knowledge, this is the first Korean study to investigate the association between hemoglobin level and incident hypertension with causality. Cross-sectional studies have shown a positive relationship between hemoglobin concentration and hypertension or high blood pressure, but the direct impacts of higher hemoglobin levels on incident hypertension have not been investigated.

This study showed the significant cross-sectional association between higher hemoglobin concentrations and hypertension and blood pressure, after stratifying the population according to age (younger and older than 60 years of age).

However, after excluding participants with hypertension, the longitudinal association showed a different pattern from the cross-sectional results. This finding may suggest the necessity for improved clinical treatment plans for both hypertensive and normotensive patients. Unlike previous studies, the current study controlled for baseline SBP, meaning that the results were less influenced by factors closely related to hypertension.

Ⅴ. CONCLUSION

The results of this cross-sectional and longitudinal study showed an association between hemoglobin concentrations and hypertension in a rural Korean population. Cross-sectional analysis revealed a significant association between higher hemoglobin concentration and the prevalence of hypertension and blood pressure among participants under 60 years of age, after adjusting for age, BMI, alcohol intake, smoking status, regular physical activity, serum BUN, creatinine, diabetes, and hypercholesterolemia. Even after excluding participants with hypertension at baseline, higher hemoglobin levels were significantly associated with higher SBP and DBP in participants less than 60 years of age.

Longitudinal analysis revealed a significant trend of increasing SBP and DBP according to baseline hemoglobin quartiles in both sexes. However, after adjusting for age, BMI, alcohol intake, smoking status, regular physical activity, serum BUN, creatinine, diabetes, hypercholesterolemia, and baseline SBP, the association between higher hemoglobin levels and incident hypertension was non-significant.

Therefore, the results of the current study suggest that higher hemoglobin concentrations were not associated with the development of hypertension in

a healthy Korean population. Further studies are necessary to determine if increased hemoglobin levels are the main cause of hypertension, by explaining the underlying biology and causal pathway.

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국문요약

헤모글로빈 농도와 고혈압 발생률과의 관련성: 일반인을 대상으로 한 코호트

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배경 및 목적

고혈압은 심혈관 질환 발생을 일으키는 원인 중에 하나이다. 고혈압의 예방을 위해 식습관과 생활습관 등 여러 원인들이 연구된 바 있다. 최근 문헌들은 정상 범위에서 높은 헤모글로빈과 고혈압 및 높은 혈압 수치가 밀접한 관련이 있다고 보고하였다.

따라서 강화 주민을 대상으로 모집한 코호트 자료를 가지고 정상 범위 내에서의 높은 헤모글로빈과 고혈압 유병 및 발생률을 알아보고자 하였다.

연구 방법

본 연구는 평균 56.6세의 강화에 거주하는 일반인 4899명의 KoGES 코호트 자료를 활용하였다. KoGES 코호트 자료는 현재도 진행되고 있는 코호트이며, 본 연구에 사용한 데이터는 2006년부터 2013년까지 모집한 자료이다. 총 4899명 중 과거에 심근경색증이나 뇌졸중이 있었던 298명과 비정상적으로 낮은 헤모글로빈을 가진 215명 (남 <13 g/dl, 여 <11 g/dl)을 제외하여 4493명(남 1,684명, 여 2,809명)을 이용하여 단면연구를 진행하였다. 종단 연구 시, 단면연구에서 활용된 데이터 중 현재 고혈압을 가지고 있는 1,159명과 반복측정 조사에 임하지 않은 1,540명을 추가로 제외하여 총 1,794명을 활용하여 분석하였다. 고혈압은 수축기 혈압 140 mmHg 이상, 이완기 혈압 90 mmHg 이상이거나, 고혈압 약을 복용하고 있는 군으로 정의하였다.

연구 결과

평균 헤모글로빈 수치는 고혈압이 없는 군보다 고혈압 있는 군에서 유의하게 높았다 (p =0.003 for men, p=0.015 for women). 단면연구 결과, 60세 미만 남자에서 나이, 성별, 체질량 지수, 생활습관, 신기능 수치, 당뇨와 고지혈증을 보정한 후 헤모글로빈 1SD 증가 시 고혈압 유병일 오즈가 1.16 (95% CI 0.96−1.40)배이었다. 반면, 60세 미만 여자에서 나이, 성별, 체질량 지수, 생활습관, 신기능 수치, 당뇨와 고지혈증을 보정한 후 헤모글로빈 1SD 증가 시 고혈압 유병일 오즈가 1.28 (95% CI 1.09−1.50)배로 유의한 관련성을 보였다. 60세 이상의 남녀에서는 보정 후 높은 헤모글로빈과 고혈압 유병과 유의한 관련성을 보이지 않았다.

종단 연구에서는 혼란변수를 보정 한 후 60세 미만의 남자에서 헤모글로빈 1SD 증가 시 고혈압 발생 비교위험도가 0.96 (95% CI 0.85−1.09)배, 여자에서 1.00 (95% CI 0.91−1.10)배로 모두 유의하지 않았다. 60세 이상의 남녀에서도 보정 전 후 모두 유의한 관련성을 보이지 않았다.

결론

본 연구는 헤모글로빈 수치와 고혈압간의 관련성을 보고자 하였다. 단면연구에서는 기존의 선행연구와 비슷하게 60세 미만의 여자에서 헤모글로빈이 높아질수록 고혈압 유병 오즈가 유의하게 높았고, 헤모글로빈과 혈압 수치와의 관련성도 유의하게 나타났다. 하지만, 종단연구에서는 연령대 상관없이 헤모글로빈과 고혈압 발생과의 관련성이 유의하지 않았다. 따라서 고혈압과 높은 헤모글로빈과의 관련성이 있지만, 높은 헤모글로빈이 고혈압의 발생원인이라고 말하긴 어렵다.

핵심되는 말: 헤모글로빈, 고혈압, 코호트 연구, 한국인

Appendix

Table S1. Baseline characteristics of study participants by exclusion and inclusion

Variables (n=4708)	Exclusion (n=215)	Inclusion (n=4493)	p value
Age, year	59.9 ± 12.0	56.6 ± 9.0	<.001
Body mass index, kg/m^2	23.3 ± 3.7	24.6 ± 3.1	<.001
Hemoglobin, g/dl	11.0 ± 1.4	13.8 ± 1.3	<.001
Systolic blood pressure, mmHg	117.8 ± 19.7	120.2 ± 17.6	0.085
Diastolic blood pressure, mmHg	69.8 ± 10.9	74.0 ± 10.5	<.001
Total cholesterol, mg/dl	178.0 ± 34.8	196.5 ± 34.1	<.001
Triglyceride, mg/dl	98.5 (75.0- 133.0)	123.0 (88.0- 175.0)	<.001
Fasting glucose, mg/dl	92.8 ± 15.4	96.6 ± 19.6	0.001
Serum blood urea nitrogen, mg/dL	16.2 ± 5.7	15.6 ± 4.3	0.177
Serum creatinine, mg/dL	1.0 ± 0.3	1.0 ± 0.1	0.002
Alcohol intake			
Former/non drinking	129 (60.0)	2689 (59.9)	1.000
Current drinking	86 (40.0)	1801 (40.1)	
Smoking status			
Former/Non-smoking	190 (88.4)	3908 (87.0)	0.636
Current smoking	25 (11.6)	583 (13.0)	
Physical activity			
No	141 (65.6)	2893 (64.4)	0.786
Yes	74 (34.4)	1597 (35.6)	
Hypertension			
No	143 (66.5)	2953 (65.7)	0.870
Yes	72 (33.5)	1540 (34.3)	
Diabetes			
No	183 (85.1)	3869 (86.1)	0.755
Yes	32 (14.9)	624 (13.9)	
Hypercholesterolemia			
No	178 (82.8)	2999 (94.4)	<.001
Yes	37 (17.2)	1494 (33.3)	

Data expressed as means ± standard deviation, median (25 to 75%), or numbers (%)

Table S2. Mean differences of hemoglobin concentration according to controlled hypertension and uncontrolled hypertension

Baseline hemoglobin, g/dL	Controlled hypertension		Uncontrolled hypertension		p-value
	No.	Mean ± SD	No.	Mean ± SD	
In cross-sectional data					
Total	800	13.8 ± 1.3	258	13.8 ± 1.4	0.959
Men	294	14.9 ± 0.9	88	15.1 ± 1.0	0.187
Women	506	13.1 ± 0.9	170	13.1 ± 1.0	0.993
In longitudinal data					
Total	110	13.8 ± 1.2	10	13.9 ± 1.5	0.785
Men	47	14.9 ± 0.8	4	15.5 ± 0.3	0.146
Women	64	13.1 ± 0.8	6	12.9 ± 0.9	0.652

SD: standard deviation; Controlled Hypertension: taking hypertensive medication and maintain normal blood pressure; Uncontrolled Hypertension: taking hypertensive medication, but abnormally high blood pressure