Original Article

Hemoglobin and ferritin concentrations are positively associated with blood pressure and hypertension risk in older adults: a retrospective cross-sectional study, Sharpeville, South Africa

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Background and Objectives: We aimed to determine the association between Hemoglobin (Hb) and ferritin with blood pressure (BP) and risk of hypertension (HTN) among elderly South African adults in four time points over a period of 10 years. **Methods and Study Design:** We used the data source from the Sharpeville Project conducted among the elderly in Sharpeville, South Africa (SA). A total of 275 subjects from the 2004 data source were included. Among these, data were available for 251, 114, and 81 subjects in 2007, 2012, and 2014 respectively. Confounding factors included age, BMI, sodium intake, high-sensitivity C-reactive protein (hs-CRP), and serum total cholesterol. Linear and logistic regressions were used to investigate the Hb and ferritin associations with BP and HTN risk. **Results:** Mean age in 2004, 2007, 2012, and 2014 was 72.8±8.66, 75.8±7.28, 80.2±9.54, and 83.2±8.98 respectively. In the unadjusted model, systolic BP (SBP) and diastolic BP (DBP), after 132.2 and 83.6 mmHg, increased by 0.57 and 0.72 mmHg respectively for each increment increase in Hb. In the adjusted model, slope coefficients remained statistically significant. Adjusted OR (95% CI) for the highest quartile of Hb (Q4) compared to the first quartile (Q1) in 2004 (p<0.001) and 2007 (p=0.017) were 2.81(2.12-4.83) and 2.58 (1.18-5.65) respectively. Those in Q4 of ferritin had OR (95% CI) of 1.85(1.32-3.73) in 2004 (p<0.001) and 2.20 (1.24-4.04) in 2007 (p<0.001) compared to Q1. **Conclusions:** Consistencies between the results from both variables suggest that some part of these positive associations could be iron dependent. Caution should be taken about unmonitored iron supplements consumption among older adults particularly those with elevated BP or on antihypertensive medications.

Key Words: blood pressure, ferritin, hemoglobin, hypertension, iron

INTRODUCTION

The 2018 guidelines from the European Society of Cardiology and the European Society of Hypertension (ESC/ESH) define hypertension (HTN) for younger, middle-aged, and older adults as the systolic blood pressure (SBP) levels of at least 140 mmHg and/or diastolic blood pressure (DBP) levels of at least 90 mmHg.[1] However, recently released guideline from the American College of Cardiology (ACC) and American Heart Association (AHA) lowered this cut-off to 130/80 mmHg.[2] HTN is a global public health challenge. Every year, it contributes to at least 45% and 51% of deaths due to heart disease and stroke respectively.[3] The relationship between blood pressure (BP) and cardiovascular risk is continuous and starts with SBP levels of as low as 115 mmHg.[1] It is estimated that after BP of 115/75 mmHg, risk for cardiovascular events increase by 100% with every increment of 20/10 mmHg.[4]

In 2010, it was estimated that 31% of the total adult population in the world suffered from HTN (BP ≥140/90 mmHg or using antihypertensive medications). The prevalence was 28.5% in high-income countries and 31.5% in low- and middle-income countries.[5] Africa, with 46% of adults aged 25 and above having HTN, has the highest prevalence rate amongst all World Health Organization (WHO) regions.[4] The results of the Study on Global Ageing and Adult Health (SAGE) by WHO with more than 35,000 subjects aged 50 and over in six countries including South Africa (SA), showed that 71% of respondents from SA had HTN (≥140/90 mmHg) with only 38% being aware of their condition. Antihypertensive medica-

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tions were effective in only 24% of these respondents.[4] Despite the efforts made by public health institutes to lower the prevalence of HTN, it continues to grow particularly in low- and middle-income countries. Overweight and obesity, high levels of sodium intake, a sedentary lifestyle, and alcohol consumption are well-known behavioral risk factors of HTN.[2] However, primary HTN is a multi-factorial disorder with a complex interplay of behavioral and pathophysiological factors influencing its etiology.[6] Acquiring an in-depth knowledge about factors that are associated with increased BP would help understanding the pathophysiology and improving the management of HTN.

There is evidence that iron status indicators such as Hemoglobin (Hb) and ferritin might be associated with high BP levels. Hb concentration has shown a positive link with BP in nonanemic adults.[7,8] Moreover, administration of erythropoietin, a hormone that promotes red blood cell mass and Hb concentration, has been associated with elevated BP.[9] Hb is also a prominent determinant of whole blood viscosity.[7,8] Evidence also exists of a positive relationship between serum ferritin concentration and increased BP.[10] Ferritin, besides being a well-known biomarker for iron status, is an acute phase reactant and an indicator of systemic inflammation.[11] Systemic inflammation is associated with arterial stiffness and acute phase proteins have shown association with arterial stiffness, incidence of myocardial infarction, and development of HTN.[12] Therefore, assessing the association of both variables with BP, while adjusting for important confounding factors that have not been adjusted for in previous studies, such as daily sodium intake and high-sensitivity C-reactive protein (hs-CRP) concentrations, would shed more light on the potential role of iron in these associations. This is particularly important among older adults because the association between Hb and serum ferritin concentrations has not previously been investigated in the elderly population (≥65 years). Based on this background, we aimed to cross-sectionally determine the association between Hb and ferritin with BP and risk of HTN among a sample of free-living South African elderly in four time points over a period of 10 years.

METHODS

We used the data source from the Sharpeville Integrated Nutrition Project (SINP) which was conducted among the elderly who voluntarily attended a faith-based day-care center on weekdays in Sharpeville, SA. The project included periodic dietary assessments, physical measurements, and blood analyses in 2004 (baseline), 2007, 2009, 2012, and 2014.[13] The study protocol was approved by the University of the Witwatersrand Medical Ethics Committee for Research involving Human Subjects (M070826) and the Vaal University of Technology Senate Research and Innovation Committee (20140827-1ms), and was conducted according to the ethics guidelines of the Declaration of Helsinki. Participation was voluntary, and participants gave consent by signing the consent form or by a fingerprint in the presence of a witness for illiterate respondents. Data for BP, body weight, height, Hb concentration, daily sodium intake, hs-CRP concentration, and serum total cholesterol (TC) concentration were available at baseline (2004), 2007, 2012, and 2014. Data for serum ferritin were available in 2004, 2007, and 2012 but not in 2014. Participants with available data on these variables were selected out of the data source. Participants in each time point were selected only if they had available data in the preceding time points. Subjects who were on antihypertensive medications at any of the evaluation time points were not selected. A total of 275 subjects from the 2004 data source (46 men and 228 women) were included and analyzed. Among these subjects, data were available for 251 subjects in 2007, 114 subjects in 2012, and 81 subjects in 2014.

BP was measured while participants were seated quietly in a chair with back support, with their both feet flat on the floor for at least 15 minutes before the measurement. A Tensoval Hartmann® duo control monitor was used on the right arm to obtain two readings. The second measurement was taken within 10 minutes of the first. The two BP readings of each individual were averaged to obtain the BP level in each time point. For the purpose of the current study, subjects were defined as hypertensive if SBP was ≥130 mmHg or if DBP was ≥80 mmHg, according to the ACC/AHA guidelines.[2] Daily sodium intake was obtained from three consecutive 24-hour dietary recalls from Sunday to Tuesday in all the time points.

Details on blood collection and storage procedures have been described elsewhere.[14] Serum ferritin was measured using immunoturbidometric method; AIA FERRTM, Tosoh Corporation, Yamaguchi, Japan. Hb concentration was measured by cyanomethaemoglobin colorimetric method; Sysmex, Randburg, SA. The data for hs-CRP were used as an inflammatory indicator which may confound ferritin-BP association (hs-CRP; immunoprecipitation; KonelabTM). The Konelab 20i random access automated clinical chemistry system was used for TC. The measuring principles of the Konelab 20i are colorimetric and turbudimetric. Weight and height were measured for all participants at baseline and at follow-up surveys. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters (kg/m^2).

Statistical analysis

Statistical analyses were conducted using the PASW Statistics (v18.0.0, SPSS Inc). For describing the baseline characteristics of subjects, we used mean and standard deviation (SD). Independent samples t-test was used to compare means between men and women in each time point. For the comparison between mean values for men, women, and total participants among different time points, repeated measures analysis of variance (ANOVA) was performed. Due to drastic decrease in the number of subjects in 2012 and 2014 linear regression analyses were performed only for 2004 and 2007 data. Simple regression and multivariate linear regression analyses were used to find unadjusted and adjusted associations of ferritin and Hb with SBP and DBP in 2004 and 2007. In order to detect the smallest model that fitted the data the best, we performed a stepwise model selection to drop the terms that were not predictive in the model. Interactions were not allowed in linear models. The stepwise selection process leaded us to a model with five covariates including

BMI, dietary sodium Intake, age, hs-CRP, and serum TC. We tested the unadjusted and adjusted association between ferritin and Hb in 2004 and 2007 with SBP and DBP in the respective years using Regression ANOVA. Ferritin and Hb were further assessed by linear regression to assess the extent to which ferritin and Hb predict the changes in SBP and DBP. For determining odds ratios (OR) and 95% confidence intervals (95% CI) for HTN in association with Hb and ferritin concentrations, logistic regression was used, and effects of confounding factors were adjusted for in multivariate models.

RESULTS

Characteristics of the study population

The SINP included a total number of 359 subjects from whom 275 (76%) met the eligibility criteria to be included in our baseline analysis. Included subjects were black (100%), lived in brick houses (99%) with ≤two rooms (29.5%), three to four rooms (40.5%), or more than four rooms (30%). The majority of participants had lived in Sharpeville for more than five years and had access to clean water, electricity, and waste removal facilities. Among the 275 subjects included in baseline analysis, 182 subjects (66.18%) had either SBP ≥130 mmHg or DBP ≥80 mmHg or both. None of these 182 subjects reported use of antihypertensive medications. The BMI indicated 3.3% underweight, 18.5% normal weight, 37.5% overweight, and 40.7% obese.

Among those included in baseline analysis (n=275), 251, 114, and 81 subjects met inclusion criteria in 2007, 2012, and 2014 respectively. Characteristics of participants in each time point are shown in Table 1. The mean age in 2004, 2007, 2012, and 2014 was 72.8±8.66, 75.8±7.28, 80.2±9.54, and 83.2±8.98 respectively. The mean Hb concentration for the total cohort in 2004 was 13.3±2.95 g/dL, followed by 13.6±1.53 g/dL in 2007, 13.0±2.61 g/dL in 2012, and 13.6±1.42 g/dL in 2014. Hb concentration among all participants was not significantly different among different time points (p=0.09). Between the two genders, Hb concentration was higher among men in all four time points but the difference was only significant in 2007 (p=0.005) and 2014 (p=0.01). Ferritin concentrations of total participants were significantly different among different time points (p=0.04) so that in 2012 (103±86 ng/mL) was lower compared to 2004 (134±115 ng/mL) and 2007 (133±135 ng/mL). Moreover, in all time points, men had higher ferritin concentrations than women. Ferritin data was not available for 2014.

The mean SBP and DBP values for the total cohort was above the HTN threshold (SBP ≥130 mmHg and/or DBP ≥80 mmHg). Mean DBP of the total participants were significantly different among the four time points (p<0.001) so that mean DBP in 2012 (82.1±23.1) and 2014 (82.0±21.4) were significantly lower than those in 2004 (93.5±31.5) and 2007 (89.9±17.4). The mean BMI of total participants was within the Class I obesity range (30.0-34.9 kg/m^2) in all time points. There was not any statistically significant difference among mean BMI in different time points. Regarding BMI differences between the two genders, women generally had grater BMI values than men.

Serum TC concentrations were generally higher among women compared to men in all time points with the difference being significant in 2004 (p=0.02), 2007 (p=0.01), and 2012 (p=0.01). In none of the evaluation time points, did the mean serum TC concentrations exceed the desirable concentration of <5.172 mmol/L (200 mg/dL). The mean hs-CRP values in all time points were within the range which has been suggested to confer an additional risk for developing HTN (>3 mg/L).[15]

Association between Hb and ferritin with SBP and DBP

Both Hb and ferritin could significantly explain the variations of SBP and DBP among the total participants (Table 2). When the only variable in the model was either Hb or ferritin, Hb seemed to explain SBP and DBP variations to a greater magnitude compared to ferritin. For example, variations in SBP values in 2004 were 10% explained by Hb (R squared=0.10) vs 8.7% by ferritin (R squared=0.087). Similarly, DBP value changes in 2004 was 12.7% (R squared=0.127) and 5.4% (R squared=0.054) explained by Hb and ferritin respectively. The same pattern was true for values of the year 2007.

When age, BMI, sodium intake, serum TC, and hs-CRP were included in the multivariate model, R squared values remained significant for both Hb and ferritin, and the multivariate model had a stronger relationship with SBP and DBP. In other words, adding these variables could improve the fit of the model. So that, R squared of ferritin in 2004 and 2007 increased from 0.08 and 0.02 in simple model to 0.29 and 0.06 in multivariate model when tested for SBP, and from 0.054 and 0.029 to 0.39 and 0.33 when tested for DBP. The same pattern was observed for Hb. For example, SBP value variations in 2004 were 10% explained by Hb in the unadjusted model (R squared=0.10) vs 27% by the multivariate model including age, sodium intake, hs-CRP, serum TC, and BMI (R square=0.27).

To assess the extent to which ferritin and Hb predict the changes in SBP and DBP, association of ferritin and Hb in 2004 and 2007 with SBP and DBP in the respective years were further assessed by Linear Regression for the coefficient of SBP and DBP changes (Table 2). In unadjusted and adjusted analyses, the slope coefficients (β) for ferritin were clinically negligible, although the models were statistically significant. Hb showed greater slope coefficients compared to ferritin. In the unadjusted model, the slope coefficient for 2004 Hb was 0.57 and 0.72, which means that starting from SBP of 132.2 mmHg and DBP of 83.6 mmHg, SBP and DBP increase by 0.57 and 0.72 mmHg respectively for each increment increase in Hb. The unadjusted model in 2007 showed that after 136.1 mmHg and 80.7 mmHg, SBP and DBP increase by 0.45 and 0.66 mmHg respectively for every 1 g/dL of increase in Hb. After adding age, BMI, sodium intake, serum TC, and hs-CRP values slope (regression) coefficients remained significant for both ferritin and Hb. For ferritin, the magnitude of the coefficient and the constant values were comparable to the unadjusted model. However, for Hb, the constant values were considerably lower and regression coefficients were considerably greater in the adjusted model (Table 2).

Table 1. Baseline characteristics of the study population

	2004 (total: 275, women: 228, men: 46)				2007 (total: 251, women: 211, men: 40)			
	Total	Women	Men	p^*	Total	Women	Men	p^*
Age (years)	72.8 (8.66)	72.7 (9.07)	72.8 (6.30)	0.94	75.8 (7.28)	75.9 (7.39)	74.9 (6.72)	0.52
BMI (kg/m^2)	31.0 (9.28)	31.3 (7.10)	29.4 (16.6)	0.21	30.5 (6.57)	31.0 (6.52)	28.3 (6.40)	0.01
Hemoglobin (g/dL)	13.3 (2.95)	13.2 (2.85)	14.0 (3.40)	0.07	13.6 (1.53)	13.5 (1.40)	14.4 (1.92)	0.005
Ferritin (ng/mL)	134 (115)	132 (115)	144 (118)	0.51	133 (135)	126 (123)	171 (188)	0.15
SBP (mmHg)	140 (28.2)	142 (27.3)	134 (31.6)	0.08	142 (26.5)	140 (26.1)	148 (23.0)	0.07
DBP (mmHg)	93.5 (31.5)	92.7 (30.9)	95.9 (32.8)	0.52	89.9 (17.4)	88.3 (15.7)	92.7 (23.1)	0.09
Total serum cholesterol (mmol/L)	4.93 (0.98)	5.03 (0.99)	4.49 (0.76)	0.02	4.62 (1.41)	4.73 (1.45)	4.09 (0.99)	0.01
Sodium intake (mg/day)	666 (524)	631 (508)	861 (607)	0.09	741 (567)	766 (591)	638 (447)	0.18
hs-CRP (mg/L)	7.07 (4.69)	7.20 (4.77)	6.59 (4.20)	0.41	8.53 (7.20)	8.35 (7.08)	9.51 (7.94)	0.01
Total energy intake (kcal/day)	1519 (750)	1485 (609)	1530 (879)	0.06	1447 (787)	1355 (574)	1573 (836)	0.02
Dietary protein (g/day)	58.6 (34.3)	57.4 (22.1)	58.3 (80.9)	0.22	64.2 (40.2)	58.6 (34.6)	65.7 (44.1)	0.32
Dietary plant protein (g/day)	25.0 (13.5)	25.3 (15.8)	24.2 (45.2)	0.18	19.4 (10.6)	20.4 (13.9)	24.7 (16.8)	0.03
Dietary animal protein (g/day)	33.8 (28.4)	32.6 (33.5)	38.1 (9.40)	0.04	45.9 (35.1)	43.6 (29.7)	48.4 (30.1)	0.04
Dietary fat (g/day)	35.8 (21.7)	37.7 (86.1)	35.0 (30.0)	0.05	48.7 (34.5)	46.4 (57.9)	53.7 (12.8)	0.02
Dietary carbohydrate (g/day)	226 (129)	184 (170)	285 (56.4)	0.02	177 (90.8)	203 (45.4)	168 (34.8)	0.05
Dietary fiber (g/day)	13.8 (7.75)	13.7 (9.91)	14.1 (1.28)	0.13	14.7 (10.5)	14.7 (11.4)	14.6 (9.36)	0.52
Dietary vitamin B-12 (mcg/day)	2.08 (2.27)	2.23 (1.03)	2.64 (2.73)	0.25	2.47 (4.55)	2.81 (2.50)	3.01 (2.73)	0.71
Dietary folate (mcg/day)	152 (114)	146 (103)	171 (183)	0.07	228 (175)	225 (121)	302 (147)	0.05
Dietary iron (mg/day)	6.80 (4.02)	5.18 (4.10)	6.83 (5.15)	0.09	9.48 (5.19)	9.82 (2.49)	9.72 (6.60)	0.45
Dietary heme iron (mg/day)	0.63 (0.80)	0.59 (1.10)	0.68 (0.92)	0.48	0.61 (0.94)	0.75 (1.03)	0.63 (0.80)	0.09

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; hs-CRP: high-sensitivity C-reactive protein.
Data are expressed as mean (SD)
p^*: t-test, men and women in each year; p^{**}: repeated measures ANOVA, women among different years; p^{***}: repeated measures ANOVA, men among different years; p^{****}: repeated measures ANOVA, total participants among different years.

Table 1. Baseline characteristics of the study population (cont.)

	2012 (total: 114, women: 98, men: 16)				2014 (total: 81, women: 69, men: 12)						
	Total	Women	Men	p^*	Total	Women	Men	p^*	p^{**}	p^{***}	p^{****}
Age (years)	80.2 (9.54)	80.1 (10.0)	80.7 (6.69)	0.84	83.2 (8.98)	83.6 (9.45)	80.9 (5.16)	0.34	<0.001	<0.001	<0.001
BMI (kg/m^2)	30.2 (6.72)	31.0 (6.8)	25.9 (4.29)	<0.001	30.1 (5.48)	30.6 (5.64)	27.2 (3.61)	0.09	0.90	0.68	0.68
Hemoglobin (g/dL)	13.0 (2.61)	12.9 (2.75)	14.0 (1.59)	0.06	13.6 (1.42)	13.4 (1.23)	14.5 (2.05)	0.01	0.10	0.80	0.09
Ferritin (ng/mL)	103 (85.7)	94.9 (79.3)	149 (106)	0.04	-	-	-	-	0.01	0.70	0.04
SBP (mmHg)	141 (25.6)	139.3 (24.3)	145 (30.3)	0.02	138 (29.5)	137 (29.2)	146 (31.2)	0.31	0.58	0.01	0.63
DBP (mmHg)	82.1 (23.1)	81.3 (21.5)	86.7 (31.8)	0.39	82.0 (21.4)	82.1 (21.9)	81.1 (18.9)	0.87	<0.001	0.17	<0.001
Total serum cholesterol (mmol/L)	5.07 (1.30)	5.21 (1.36)	4.44 (0.75)	0.01	5.05 (1.08)	5.14 (1.10)	4.56 (0.83)	0.08	0.008	0.18	0.003
Sodium intake (mg/day)	636 (491)	634 (496)	649 (475)	0.93	766 (626)	772 (647)	731 (510)	0.83	0.12	0.44	0.29
hs-CRP (mg/L)	6.82 (8.33)	7.20 (8.96)	5.08 (4.14)	0.26	6.37 (4.40)	6.66 (4.53)	4.62 (3.08)	0.06	0.14	0.007	0.009
Total energy intake (kcal/day)	985 (420)	1050 (303)	930 (59.1)	0.02	1126 (461)	1119 (438)	1204 (530)	0.05	<0.001	<0.001	0.04
Dietary protein (g/day)	43.9 (18.7)	43.3 (16.8)	43.7 (25.7)	0.80	53.9 (25.9)	54.1 (20.4)	53.6 (22.6)	0.10	0.003	0.007	0.06
Dietary plant protein (g/day)	17.1 (8.93)	16.8 (6.45)	17.2 (3.92)	0.28	15.4 (8.20)	15.6 (9.20)	16.0 (8.29)	0.28	0.01	0.01	0.17
Dietary animal protein (g/day)	42.3 (28.6)	42.0 (30.6)	41.9 (19.1)	0.12	28.5 (16.8)	27.6 (13.1)	30.4 (21.4)	0.04	0.02	0.01	0.06
Dietary fat (g/day)	28.9 (17.5)	28.4 (23.1)	27.4 (15.7)	0.24	34.9 (27.3)	35.6 (20.6)	32.5 (29.6)	0.01	0.08	0.05	0.11
Dietary carbohydrate (g/day)	126.4 (61.0)	125 (74.5)	129 (87.6)	0.03	134 (57.8)	130 (73.4)	135 (43.8)	0.01	<0.001	<0.001	<0.001
Dietary fiber (g/day)	10.9 (7.12)	10.2 (3.13)	13.7 (53.4)	0.01	8.85 (4.94)	8.00 (2.62)	10.4 (6.10)	0.32	0.05	0.04	0.08
Dietary vitamin B-12 (mcg/day)	1.72 (1.60)	1.75 (1.74)	1.72 (0.85)	0.63	1.12 (1.29)	0.80 (1.54)	1.23 (1.02)	0.04	0.009	0.03	0.17
Dietary folate (mcg/day)	160.1 (88.8)	161 (74.5)	164 (34.7)	0.06	114 (108)	126 (70.6)	109 (130)	0.03	<0.001	<0.001	<0.001
Dietary iron (mg/day)	7.35 (3.84)	6.85 (1.34)	7.74 (4.65)	0.04	5.46 (3.66)	5.29 (2.71)	7.84 (5.81)	0.03	0.06	0.04	0.07
Dietary heme iron (mg/day)	0.41 (0.42)	0.43 (0.30)	0.41 (0.12)	0.05	0.31 (0.42)	0.32 (0.11)	0.31 (0.36)	0.16	0.003	<0.001	0.05

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; hs-CRP: high-sensitivity C-reactive protein.
Data are expressed as mean (SD).
p^*: t-test, men and women in each year; p^{**}: repeated measures ANOVA, women among different years; p^{***}: repeated measures ANOVA, men among different years; p^{****}: repeated measures ANOVA, total participants among different years.

Table 2. Association between ferritin and hemoglobin concentrations with systolic and diastolic blood pressure in 2004 and 2007

Variables	No. of participants	Unadjusted (simple regression)			Adjusted for age, BMI, sodium intake, total cholesterol, hs-CRP (Multivariate regression)		
		R squared/ constant (β)†	SE	*p*-value	R squared/ constant(β)†	SE	*p*-value
The extent SBP and DBP are explained by Ferritin and Hemoglobin							
Ferritin							
SBP 2004	275	0.087	28.1	<0.001	0.289	25.2	<0.001
DBP 2004	275	0.054	32.5	<0.001	0.392	26.6	<0.001
SBP 2007	251	0.023	27.0	0.009	0.060	30.3	0.045
DBP 2007	251	0.029	19.9	0.004	0.333	20.0	<0.001
Hemoglobin							
SBP 2004	275	0.101	28.0	<0.001	0.271	25.6	<0.001
DBP 2004	275	0.127	31.3	<0.001	0.338	28.0	<0.001
SBP 2007	251	0.063	26.5	<0.001	0.078	30.0	0.020
DBP 2007	251	0.258	17.4	<0.001	0.357	19.6	<0.001
Linear regression of SBP and DBP on Ferritin and Hemoglobin							
Ferritin							
SBP 2004	275	130.74 (0.07)†	0.01	<0.001	136.33 (0.08)	0.03	0.01
DBP 2004	275	84.88 (0.07)†	0.02	<0.001	91.95 (0.09)	0.03	0.007
SBP 2007	251	138.51 (0.03)†	0.01	0.009	133.20 (0.02)	0.02	0.03
DBP 2007	251	86.95 (0.03)†	0.01	0.004	81.65 (0.01)	0.01	0.05
Hemoglobin							
SBP 2004	275	132.24 (0.57)†	0.10	<0.001	124.20 (1.88)	0.90	0.04
DBP 2004	275	83.58 (0.72)†	0.11	<0.001	82.22 (1.12)	0.98	0.02
SBP 2007	251	136.11 (0.45)†	0.11	<0.001	111.47 (2.72)	1.56	0.08
DBP 2007	251	80.70 (0.66)†	0.07	<0.001	63.06 (2.29)	1.02	0.02

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; hs-CRP: high-sensitivity C-reactive protein.
†Constant: the intercept; β: the slope coefficient.

Association between Hb and ferritin concentrations with risk of HTN

Hb and ferritin concentrations showed significant positive associations with the risk of HTN (SBP ≥130 mmHg and/or DBP ≥80 mmHg) in 2004 and 2007 (Table 3). The OR and 95% CI for the highest quartile of Hb compared to the first quartile in the first (2004) and second (2007) evaluation time points were 2.81 (2.12-4.83) and 2.58 (1.18-5.65) respectively. Similarly, those who were in the highest quartile of ferritin concentration had an OR (95%CI) of 1.85 (1.32-3.73) in 2004 and an OR (95% CI) of 2.20 (1.24-4.04) in 2007. None of the estimated ORs (95% CI) were significant in 2012 and 2014 which has been probably due to small sample sizes in these two time points.

DISCUSSION

The present study showed a positive association between Hb and ferritin concentrations with SBP, DBP, and the risk of HTN in older adults. Few studies to date have addressed the association between BP and iron indicators. Gobel et al, in a cross-sectional study demonstrated statistically significant correlations between SBP and DBP with Hb concentration.[16] Results from the Korea National Health and Nutrition Examination Surveys (KNHNES)[7] and the study with a large group of healthy, Dutch, voluntary blood donors were also in line with our results.[8]

Results from our study suggested that SBP and DBP increase by 0.45-0.57 mmHg and 0.66-0.72 mmHg respectively for every 1 g/dL increase in Hb. Some earlier cross-sectional studies also focused on regression coefficient of BP and Hb. Results of the study by Atsma et al which involved 101,377 healthy adults were in line with our results in terms of both the positive Hb-BP association and the magnitude of the regression coefficients. They demonstrated that SBP increased 1.3 mmHg per every 1.61 g/dL (mmol/L) increase in Hb concentration among men and 1.8 mmHg per every 1.61 g/dL (1 mmol/L) increase in Hb concentration among women. Similarly, per every increment increase in Hb (1.61 g/dL), DBP increased 1.5 mmHg among men and 1.4 mmHg among women.[8] The data from the KNHNES 2008–2011 also showed that Hb concentration was positively related to SBP and DBP but with greater association magnitude compared to our results. They showed that every 1.61 g/dL (1 mmol/L) increase in Hb concentration within the non-anemic range, was associated with 2.6 mmHg increase in SBP and 3.2 mmHg in DBP in both genders.[7]

In both above-mentioned studies, the positive Hb-BP association was demonstrated in the normal ranges of Hb. In the Dutch study, Hb concentration of ≥13.5 g/dL for men and ≥12.6 g/dL for women were part of the eligibility criteria.[8] In the Korean study, BP did not associate with Hb at low Hb concentrations. In that study, the positive Hb-SBP and Hb-DBP association was only observed in men with Hb concentrations ≥13.0 g/dL and women with Hb concentrations ≥11.0 g/dL.[7] In our study, because of the small sample size, subgroup analysis based on the Hb concentration categories was not performed. Our multiple logistic regression analysis results suggested that the odds of having SBP ≥130 and/or DBP≥80 (HTN) according to Hb level does not increase significantly until after Hb concentration of >14.5 g/dL. Moreover, odds of SBP ≥130 and/or DBP ≥80 according to ferritin con-

Table 3. Odds ratio (OR) of hypertension (HTN) by hemoglobin and ferritin

		Hemoglobin				Ferritin			
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
2004		3.0-12.0	12.0-13.1	13.1-14.6	14.6-24.0	6.0-55.0	55.0-99.3	99.4-18	186-711
	OR† (95% CI)	Ref	0.77 (0.39-1.55)	2.09 (0.99-4.37)	2.81 (2.12-4.83)	Ref	0.90 (0.45-1.80)	1.74 (0.84-3.59)	1.85 (1.32-3.73)
	p-value		0.48	0.05	<0.001		0.77	0.13	<0.001
	(n)	(65)	(65)	(67)	(67)	(66)	(67)	(70)	(70)
2007		7.5-12.7	12.7-13.7	13.7-14.5	14.5-18.2	5.70-50.5	50.5-98.3	98.3-161	161-981
	OR† (95% CI)	Ref	1.41 (0.71-2.79)	1.38 (0.65-2.95)	2.58 (1.18-5.65)	Ref	0.96 (0.48-1.95)	2.93 (1.38-6.24)	2.20 (1.24-4.04)
	p-value		0.32	0.39	0.017		0.92	0.05	<0.001
	(n)	(62)	(76)	(51)	(58)	(62)	(63)	(63)	(62)
2012		8.1-12.0	12.0-12.9	12.9-13.8	13.9-37.3	3.80-38.8	38.8-82.3	82.3-148	148-469
	OR† (95% CI)	Ref	2.22 (0.51-9.59)	1.27 (0.34-4.72)	1.75 (0.39-7.73)	Ref	2.0 (0.40-9.90)	1.40 (0.68-3.40)	1.45 (0.12-5.67)
	p-value		0.28	0.71	0.46		0.39	0.12	0.23
	(n)	(18)	(18)	(21)	(15)	(18)	(15)	(18)	(21)
2014		9.5-12.9	12.9-13.7	13.7-14.5	14.51-17.20	-	-	-	-
	OR† (95% CI)	Ref	2.94 (0.78-11.09)	1.90 (0.52-7.0)	1.63 (0.43-6.11)	-	-	-	-
	p-value		0.11	0.33	0.46				
	(n)	(20)	(23)	(20)	(18)				

†Adjusted Odds Ratio (OR) for Hypertension (HTN) when HTN is defined as systolic blood pressure≥130 and/or diastolic blood pressure ≥80, adjusted for body mass index (BMI), dietary sodium intake, age, high-sensitivity C-reactive protein (hs-CRP), and serum total cholesterol level.

centration increased only for those with ferritin concentrations of >161.4 ng/L. In line with these results, Sung et al demonstrated among 12,033 Korean men that ferritin concentration was independently associated with the presence of a preclinical atherosclerosis biomarker called coronary artery calcium. They reported that those with ferritin concentrations of >257 ng/L had a higher score for coronary artery calcium than those with ferritin of <128 ng/L.[17]

The positive association between ferritin and BP has been demonstrated by several cross-sectional studies.[10,18-20] A longitudinal study with a 4-year follow-up timing among 8,580 men demonstrated that those who developed HTN had higher concentrations of ferritin at baseline compared to those who remained normotensive.[21] Also, the risk of HTN incidence at 5-year follow-up was positively associated with elevated baseline serum ferritin concentration in Korean men.[22] Furthermore, several studies have affirmed the relationship between serum ferritin concentrations and carotid atherosclerotic plaque formation.[23-26] Every 4.5 ng/mL (10 pmol/L) increase in serum ferritin has been associated with 0.5% and 1.5% increase in coronary heart disease (CHD) risk in men and women aged 30-64 years respectively[27] and a serum ferritin concentration of 200 ng/mL has been associated with a 2.2-fold increase in the risk for myocardial infarction.[28]

Putative mechanisms of the positive association between Hb and ferritin with high BP have been shown in Figure 1. Theoretically, when ferritin is saturated, free iron reacts with hydrogen peroxide (H_2O_2) by oxidizing Fe^{2+} to Fe^{3+} to produce a hydroxyl radical. These free radicals cause oxidative stress and lead to lipid peroxidation, low-density lipoprotein (LDL) cholesterol oxidation, and oxidative damage to the coronary arteries.[27,29] Moreover, during oxidative stress, superoxide radicals increase the release of iron from ferritin and its oxidation to Fe^{3+}. This suggests a possible pro-atherosclerotic role of increased ferritin which possibly contributes to the ferritin-BP positive association.[30]

Ferritin may also impose its pro-atherosclerotic effects though an iron unrelated mechanism.[17] Ferritin is an acute phase reactant and is affected by inflammatory processes irrespective of the iron store status.[31] In our study, serum ferritin had a weak positive correlation with hs-CRP concentrations (data not shown), which suggests a possible inflammation-mediated association between ferritin and BP. On the other hand, the consistency between the overall results obtained for ferritin and Hb reaffirms an iron mediated effect on BP.

The effect of Hb and ferritin incremental increase on BP was lower than 1 mmHg in the present study. However, these effects already mean a substantial difference in cardiovascular events. Several meta-analyses have shown that an SBP decrease of 1 mmHg decreases the risk of stroke by 5%.[32] At the population level, it has been estimated that 1 mmHg decrease in SBP among African American and white US populations aged 45-64 prevents about 9,338 incident heart failure events, 6,210 incident CHD events, and 3,761 incident stroke events annually. Furthermore, the estimated benefits from decrements in SBP were greater for African-Americans than for whites; for example, every 1 mmHg SBP reduction prevents 7.0 additional heart failure events per 100,000 person-years in African Americans compared to whites.[33] Again, at the population level, it has been estimated that a 2 mmHg reduction in DBP would decrease the risk of CHD and stroke by 6% and 15% respectively.[34]

The positive association between Hb and BP could be explained by several mechanisms. One possible reason is the positive association between arterial stiffness, measured as increased pulse wave velocity (PWV), and Hb which, in turn, results in elevation of SBP and DBP.[35] The other possible mechanism is the association between Hb and blood viscosity. Blood viscosity increases in parallel with blood hematocrit that is highly correlated with Hb concentration.[36] Blood viscosity is associated with peripheral resistance which, in turn, might lead to increased BP.[37] However, the effects of increased blood viscosity on BP might differ between hypertensive and normotensive individuals.[37,38] It has been suggested that normotensive individuals who have normal endothelial function are able to compensate for the viscosity-induced vascular resistance.[39] In accordance with these potential mechanisms, our results demonstrated that when the only determinant in the linear model was Hb, the positive association between Hb and BP started at above normal BP levels in all analyses which were at least 132 mmHg for SBP and 81 mmHg for DBP.

The other possible mechanism that may explain our results is the inverse association between Hb and B-type natriuretic peptide (BNP). BNP and its molecular precursor (proBNP) are released from the heart to regulate BP and fluid balance. These peptides counteract the effects of renin secretion, inhibit aldosterone secretion, increase glomerular filtration rate and urinary sodium excretion, and cause an overall reduction in BP and extracellular fluid volume.[40] It has been shown that Hb concentrations are inversely associated with plasma BNP concentrations and independently predict plasma concentrations of this peptide and its precursor. Also, moderate anemia has shown association with a 1.7-fold increase in proBNP concentrations.[41,42] A nested case-control study of 6,238 individuals from a Danish general population, demonstrated that Hb concentrations of <12 g/dL in women and <13 g/dL in men, were associated with increased circulating proBNP concentrations.[42] Based on the positive association between Hb concentrations of <12 g/dL and proBNP concentrations, we assume that the difference in the odds of HTN between the first (~<12 g/dL) and the last quartile of Hb in our results is partly attributed to the plasma BNP concentrations.

Overall, our results for the association between ferritin and BP were in line with those of Hb. The reason for the small, clinically insignificant linear regression coefficients for ferritin is probably clinical insignificance of every 1-ng/mL incremental increase in ferritin concentration. Therefore, a proposed incremental increase of 10 ng/mL in ferritin concentration would result in a clinically considerable increase in SBP and DBP which is comparable to the extent seen for Hb. This also can explain the discrepancy between linear regression analyses for ferritin, where results are clinically negligible, with the results from logistic regression, where those in the last quartile of ferritin concentration have significant greater

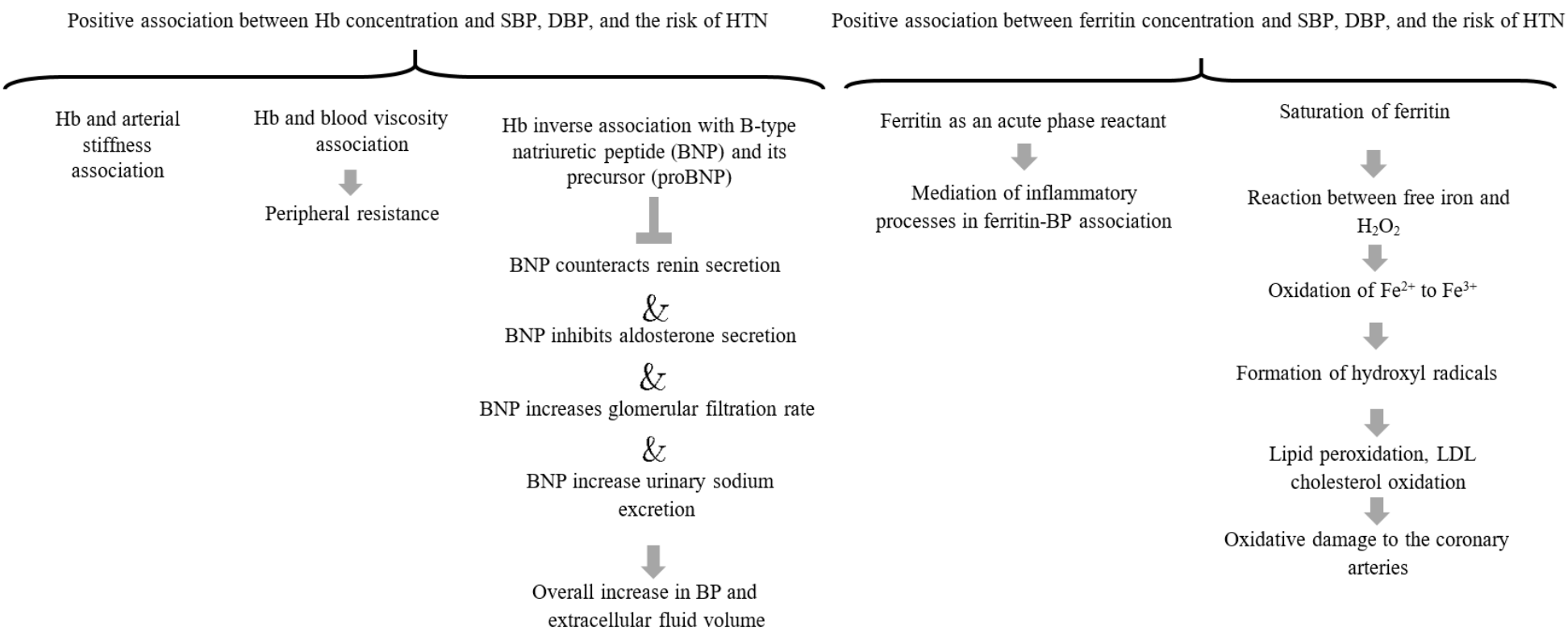

Figure 1. Conceptual diagram of the putative mechanisms of the positive association between Hb and ferritin with high blood pressure.

odds of being hypertensive compared to those in the first quartile.

This study has several strengths. Firstly, we were able to adjust the effects of dietary sodium intake and hs-CRP concentrations besides other important confounding factors including age, BMI, and serum TC. Secondly, this is the first study that reported the association between Hb and ferritin concentrations with BP at the same time to cast more light on whether there are iron mediated effects in the association between Hb and ferritin with BP. Analyses of the data for the same subjects in two time points (2004 and 2007) reinforce cross-sectional results and also suggest the sustainability of the Hb-BP and ferritin-BP associations. Moreover, this is the first study that reports the association between Hb and ferritin with BP among older adults.

This study has some limitations including domination of female subjects in the study population which made it impossible to interpret gender-based subgroup regression analyses, leading to lack of comparisons between women and men. However, it has been suggested that there is no significant gender-based difference in BP after menopause. Also, a recent cardiovascular risk analysis from the National Health and Nutrition Examination Survey (NHANES) demonstrated no significant difference by gender at any age over age of 50.[43,44] Therefore, it is unlikely that gender-based differences in BP regulation have affected the results of this study. Another limitation is that a definite conclusion cannot be drawn about any causal relationship between Hb and ferritin concentrations with BP, which is due to the cross-sectional design of the analyses. Finally, our sample size shrank drastically down in the last two time points although the results were in line with the results from 2004 and 2007 data.

Conclusion

The findings reported here provide evidence of the positive association between Hb and ferritin with SBP and DBP, particularly within HTN ranges. Consistencies between the results from both variables (ferritin and Hb) suggest that at least some part of these positive associations is mediated by iron dependent mechanisms. Older adults and their health care providers need to be informed about the health concerns associated with unmonitored consumption of iron supplements, particularly in those who have elevated BP or those using antihypertensive medications.

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AUTHOR DISCLOSURES

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