

Markers of iron status, blood pressure and incident hypertension among Chinese adults

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Haemoglobin;
Hypertension

Abstract *Background and aims:* The evidence on the relationship between markers of iron, blood pressure and hypertension are limited and inconsistent. This prospective cohort study aimed to investigate the relationship of serum ferritin (SF), transferrin, soluble transferrin receptor (sTFR) and haemoglobin on blood pressure and incident hypertension in the China Health and Nutrition Survey (CHNS) study.

Methods and results: We studied 8337 adults aged 18 years old or above from CHNS in 2009 to investigate the association of markers of iron and blood pressure (BP). Among them, 4509 non-hypertensive participants who completed follow up were included to investigate the association of markers of iron and hypertension development. Linear regression model was used to assess the association between markers of iron and BP. Cox regression model was used to examine the association of markers of iron and hypertension development. SF and serum sTFR concentration had a non-significant effect on incident hypertension. Transferrin and haemoglobin concentrations were positively associated with incident hypertension. Compared to the participants with the lowest tertile of transferrin, those with the highest tertile had a higher risk of developing hypertension [HR: 1.26, 95% CI (1.04, 1.53), $P = 0.017$]. Similarly, participants with the highest tertile of haemoglobin had a significantly higher risk of incident hypertension [HR: 1.27, 95% CI (1.01, 1.59), $P = 0.038$].

Conclusion: The current study found that haemoglobin and transferrin levels were positively associated with blood pressure and incident hypertension. Further research in different ethnic groups is required to confirm the association of the full range of markers of iron with BP and incident hypertension.

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Introduction

Hypertension is the leading risk for disability and death worldwide and accounted for over 10.5 million deaths in

2016 [1]. It is estimated that the world's prevalence of hypertension will increase from 26.4% in 2000 to 29.2% by 2025 [2]. Therefore, the prevention and prediction of hypertension is essential for decreasing the global disease burden and cardiovascular mortality.

Increasing evidence has suggested that iron metabolism plays an important role in the development of hypertension [3–9]. Serum ferritin (SF), transferrin, soluble transferrin receptor (sTFR), and haemoglobin are the most widely used biomarkers in epidemiological and clinical

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studies to evaluate body iron stores. Two cross-sectional studies in Korea both suggested that SF was positively associated with the prevalence of hypertension [3,4]. One case-control study in Italy found that SF was higher in men with essential hypertension [5]. Furthermore, a cohort study in Korea also suggested that SF was positively associated with the prevalence of hypertension [6]. Previous studies have also suggested that haemoglobin showed a significant positive association with blood pressure and incident hypertension [8,10,11]. However, one study in Korea observed a significant positive association between haemoglobin concentrations and the prevalence of hypertension, but did not observe a significant association between baseline haemoglobin and incident hypertension in the longitudinal analysis [9]. Despite these inconsistent results, no study investigated the association of SF, transferrin, sTFR and haemoglobin with blood pressure and incident hypertension in the same population. We therefore conducted the national population-based observational study from China Health and Nutrition Survey (CHNS) to investigate the association of markers of iron (SF, transferrin, sTFR and haemoglobin) with blood pressure and incident hypertension.

Method

The China Health and Nutrition Survey (CHNS) started in 1989 and was then followed up every 2–4 years (i.e., in 1989, 1991, 1993, 1997, 2000, 2004, 2006, 2009 and 2011). We used a multistage random-cluster process to select samples in nine diverse provinces (Guangxi, Guizhou, Heilongjiang, Henan, Hubei, Hunan, Jiangsu, Liaoning and Shandong). Four counties in rural sites and two cities in urban sites were selected randomly in each province according to income levels (low, middle and high), with a weighted sampling scheme. Details of the CHNS were described in previous studies [12]. All the participants received a series of examinations including measurements of blood pressure each wave. The participants also completed a questionnaire on basic socioeconomic factors and health, nutritional and demographic measures. Blood samples were collected and tested for the first time in 2009, and the update of longitudinal datasets for 2011 and 2015 collections are underway. Prior to joining the medical screening programme, all of the participants were asked to sign the informed consent and the study was approved by the institutional review committees of the University of North Carolina at Chapel Hill, the National Institute of Nutrition and Food Safety and the Chinese Centre for Disease Control and Prevention.

In the current study, we included 9207 participants aged 18 years or older from the year 2009 when blood collection and measurement were conducted for the first time. Participants with no blood pressure measurement ($n = 462$), pregnancy status ($n = 62$), no blood assessments on SF, transferrin, sTFR, or haemoglobin ($n = 81$), and no physical examination ($n = 265$) were excluded. As a result, 8337 participants were included to investigate the association between markers of iron status and systolic

blood pressure (SBP) and diastolic blood pressure (DBP). Among them, 2530 participants were further excluded due to having hypertension at baseline (i.e., in the year 2009). In the remaining 5807 participants, 4509 participants who completed the follow-up in 2011 were included to investigate the relationship between markers of iron and hypertension development. The process of participant selection is presented in Fig. 1.

An overnight fasting blood sample was taken in the morning after at least 12 h. As presented in previous studies [13], all samples were verified and analysed in a national central lab in Beijing (medical laboratory accreditation certificate ISO 15189:2007) according to strict quality control standards [14,15]. Detailed information on the measurement method of the markers for iron has been reported in previous studies [16,17]. The SF was measured by radioimmunity on a gamma counter XH-6020 (North Institute of Bio-Tech, Beijing, China). Serum transferrin and sTFR were both measured by nephelometry on a Siemens B-type natriuretic peptide assay (Siemens, Erlangen, Germany). Whole blood haemoglobin concentrations were measured by a LH75 haematology analyzer (Beckman Coulter, Brea, CA, USA).

The primary health outcome for the current study is incident hypertension, and the secondary health outcomes are SBP and DBP. As previously reported [18], trained examiners measured the seated SBP and DBP of each participant by standard mercury sphygmomanometer on the right arm in triplicate after 10 min rest. The mean of the three measurements was used. Hypertension was defined as SBP ≥ 140 mmHg or DBP ≥ 90 mmHg, having been previously diagnosed as hypertension by a physician, or currently taking antihypertensive drugs.

Weight was measured in light clothing by a calibrated beam balance to the nearest 0.1 kg. Height was measured without shoes to the nearest 0.1 cm using a portable SECA stadiometer. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). A structured questionnaire asked by trained and experienced interviewers was used to collect information on lifestyle covariates including age, gender, education, smoking and alcohol intake. Three consecutive 24 h dietary recalls (including two weekdays and one weekend) at the individual level, or a food inventory weighting at the household level for the same three days was used to assess the dietary intake [19]. Dietary intakes of total energy, carbohydrate, protein and fat were calculated based on the Chinese Food Composition Table 2004 and 2009 [20,21].

Descriptive data are presented as mean (standard deviation) for continuous variables and number (percentage) for categorical variables. Multi-variable linear regression model was used to conduct a cross-sectional data analysis of the associations between markers of iron status and SBP and DBP. Cox regression model was used to examine the effect of markers of iron status on hypertension development. Three models were developed: Model 1: without any adjustment; Model 2: adjusted for age, gender, education level [lower than middle school (<6 years), middle school (6.1–9.0 years), high school (9.1–12 years), or

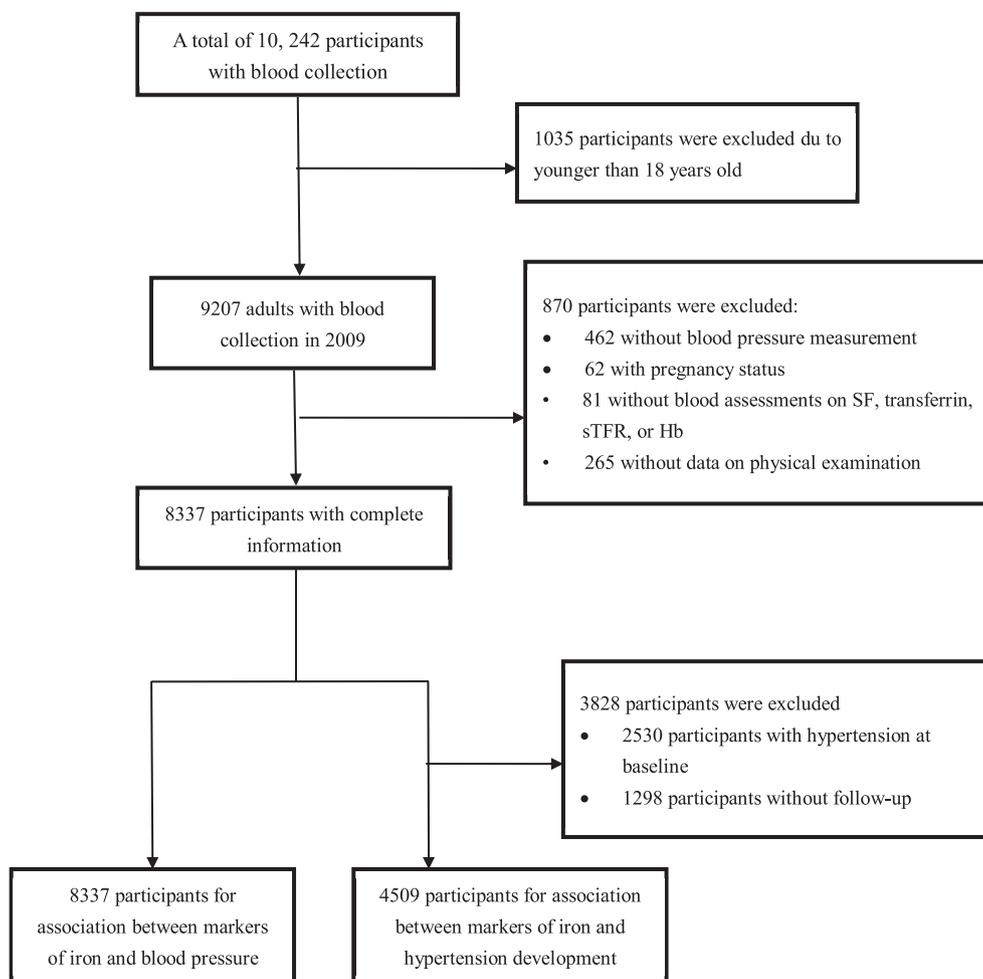


Figure 1 Flowchart of participant selection.

college/university (>12 years)], smoking status (never or ever), alcohol consumption [yes (ever drank beer/alcohol the year before the examination) or no (did not drink beer/alcohol the year before the examination)], total energy intake, protein intake, fat intake and carbohydrate; Model 3: further adjusted for hypertension (not for the effect of markers of iron status on hypertension development) and BMI (<25 kg/m², 18.5–24.9 kg/m², 25.0–29.9 kg/m², or ≥30 kg/m²).

As iron status differs in different genders [22,23], we also performed our analysis separately by sex to investigate the relationships between the markers of iron and blood pressure and hypertension development.

All statistical analysis was conducted using R 3.3.2 (R Core Team, Vienna, Austria) and two-sided *P* values of <0.05 were considered statistically significant.

Result

The characteristics of participants in the current study are presented in Table 1. A total of 8337 participants (46.9% men) with a mean age of 50.98 ± 14.97 years were

included in the analysis of the association of SF, transferrin, sTFR and haemoglobin on SBP and DBP. A total of 4509 participants (44.1% men) with non-hypertension (mean age: 49.11 ± 13.60 years at baseline) were included in the analysis of the effect of SF, transferrin, sTFR and haemoglobin on incident hypertension, with 632 incident hypertension cases being identified during the follow-up period.

The association of SF, transferrin, sTFR and haemoglobin with SBP and DBP are presented in Tables 2 and 3, respectively. There was a non-significant association between SF and SBP [highest vs. lowest Coef: 0.11 mmHg, 95% CI: −0.66–0.89; *P* = 0.776]. Compared to participants with the lowest tertile of SF, those with the highest tertile showed a significantly higher DBP (by 0.87 mmHg, 95% CI: 0.35–1.38; *P* < 0.001). Compared to participants with the lowest tertile of sTFR, those with the highest tertile showed a significantly higher SBP (by 1.78 mmHg, 95% CI: 1.10–2.46; *P* < 0.001) and DBP (by 0.75 mmHg, 95% CI: 0.30–1.20; *P* = 0.001). Compared to participants with the lowest tertile of haemoglobin, those with the highest tertile showed a significantly higher SBP (by 1.68 mmHg, 95% CI: 0.84–2.52; *P* < 0.001) and DBP (by 3.32 mmHg, 95% CI:

Table 1 Baseline characteristics of the included study participants.

Characteristic	All participants	Non-hypertension at baseline
Participants	8337	4509
Age, years	50.98(14.97)	49.11(13.60)
Gender		
Male	3914 (46.9%)	1988 (44.1%)
Female	4423(53.1%)	2521 (55.9%)
Education		
<6 years	4410 (52.9%)	2246 (49.8%)
6–9 years	2361 (28.3%)	1327 (29.4)
9–12 years	1318 (15.8%)	790 (17.5%)
>12 years	248 (3.0%)	146 (3.2%)
Current smoker		
Yes	2527 (30.3%)	1300 (28.8%)
No	5810 (69.7%)	3209 (71.2%)
Alcohol consumption		
Yes	2740 (32.9%)	1404 (31.1%)
No	5597 (67.1%)	3105 (68.9%)
Rural area		
Yes	5606 (67.2%)	3113 (69.0%)
No	2731 (32.8%)	1396 (31.0%)
BMI, kg/m ²	23.38 (3.48)	22.91 (3.21)
Total energy intake, kcal/day	2433.49 (781.55)	2451.20 (800.04)
Carbohydrate intake, % energy	62.77 (12.39)	62.71 (12.56)
Protein intake, % energy	12.03 (2.71)	12.07 (2.65)
Fat intake, % energy	24.67 (11.65)	24.60 (11.78)
SF, µg/L	137.82 (185.54)	128.25 (179.22)
Transferrin, g/L	2.87 (0.55)	2.88 (0.55)
sTFR, mg/L	1.47 (0.71)	1.47 (0.76)
Hb, g/L	141.39 (20.66)	140.25 (20.34)
Diabetes	541 (6.5%)	215 (5.0%)

Abbreviations: SF: serum ferritin; sTFR: soluble transferrin receptor; BMI: body mass index; Hb: haemoglobin.

The statistical data are shown as means (standardised deviations) for continuous variables and counts (percentages) for categorical variables.

2.76–3.87; $P < 0.001$). Compared to participants with the lowest tertile of transferrin, those with the highest tertile showed a significantly higher SBP (by 0.96 mmHg, 95% CI: 0.27–1.65; $P = 0.006$) and DBP (by 1.35 mmHg, 95% CI: 0.89–1.08; $P < 0.001$). These significant positive associations were also observed both in males and females in the subgroup analysis by gender (Tables S1, S2, S3 and S4).

The effects of SF, transferrin, sTFR and haemoglobin on incident hypertension are presented in Table 4. SF and serum sTFR had a non-significant effect on incident hypertension. Compared to participants with the lowest tertile of transferrin, those with the highest tertile had higher risk of developing hypertension [HR: 1.26, 95% CI (1.04, 1.53), $P = 0.017$]. Similarly, participants with the highest tertile of haemoglobin had a significantly higher risk of incident hypertension [HR: 1.27, 95% CI (1.01, 1.59), $P = 0.038$]. In male participants, those with the highest quartile of haemoglobin levels had a significantly higher risk of hypertension when compared to the lowest group [HR: 1.35, 95% CI (1.03, 1.77), $P = 0.030$]. However, this association was not found in female participants [HR: 1.28, 95% CI (0.97, 1.69), $P = 0.078$] (Tables S5 and S6).

Discussion

To our knowledge, this is the first study to investigate the effects of SF, transferrin, sTFR and haemoglobin on both blood pressure and hypertension development in the same population. This nationwide population-based study suggested that SF was positively associated with DBP but not SBP. Transferrin, sTFR and haemoglobin levels were positively correlated with both SBP and DBP. Furthermore, we found that levels of transferrin and haemoglobin were positively associated with risk of hypertension. Our data suggests that dysregulation of iron metabolism is an important independent risk factor for the onset of hypertension in the Chinese population.

The lack of association between SF and hypertension is inconsistent with previous studies. Two cross-sectional studies in Korea both suggested that SF was positively associated with the prevalence of hypertension [3,4]. One case–control study in Italy found that SF was higher in men with essential hypertension [5]. Furthermore, a cohort study in Korea also suggested that SF was positively associated with the prevalence of hypertension [6]. This inconsistency may be due to a number of factors, including the heterogeneity of the study populations and the study regions, as well as the research methods. The level of SF may also play an important role in the inconsistency. The majority of our study participants (3748 out of 4509) had a normal range of SF concentrations, which partly explains the non-significant association.

In our study, we found that haemoglobin levels were positively associated with blood pressure and the risk of incident hypertension, which was consistent with several previous studies. A Cross-sectional study in Japan demonstrated that haemoglobin concentrations were positively associated with the risk of incident hypertension [7]. A Dutch study reported that haemoglobin showed a significant positive association with blood pressure [10]. A Kenyan cross-sectional study suggested that haemoglobin concentrations were positively associated with blood pressure [11]. One Korean study observed that haemoglobin concentrations were positively associated with hypertension and blood pressure [8]. However, another study in Korea observed a significant positive association between haemoglobin concentrations and the prevalence of hypertension, but did not observe a significant association between baseline haemoglobin and incident hypertension in the longitudinal analysis [9]. In our study, we also firstly reported that transferrin levels were associated with blood pressure and the risk of incident hypertension, whose primary role is transporting iron safely around the body to supply growing cells.

Our study has several important strengths. The longitudinal design of the cohort enables us to examine the effects of SF, transferrin, sTFR and haemoglobin on hypertension development prospectively. Another strength is the large-scale, longitudinal, nationwide, population-based study design of the CHNS. The CHNS represents a set of large provinces which cover approximately 56% of the Chinese population, and those chosen provinces

Table 2 Associations of SF, transferrin and Hb levels with SBP in Chinese adults at baseline.

	Model 1		Model 2		Model 3	
	Coef (95% CI)	P	Coef (95% CI)	P	Coef (95% CI)	P
Serum ferritin						
Tertile 1st	Ref		Ref		Ref	
Tertile 2nd	6.53 (5.54, 7.52)	<0.001	1.80 (0.84, 2.75)	<0.001	0.35 (-0.34, 1.08)	0.344
Tertile 3rd	7.20 (6.21, 8.18)	<0.001	2.28 (1.30, 3.30)	<0.001	0.11 (-0.66, 0.89)	0.776
Trend		<0.001		<0.001		0.814
Soluble transferrin receptor						
Tertile 1st	Ref		Ref		Ref	
Tertile 2nd	1.29 (0.28, 2.30)	0.012	1.25 (0.35, 2.15)	0.006	1.03 (0.35, 1.72)	0.003
Tertile 3rd	2.64 (1.65, 3.64)	<0.001	2.51 (1.61, 3.40)	<0.001	1.78 (1.10, 2.46)	<0.001
Trend		<0.001		<0.001		<0.001
Haemoglobin						
Tertile 1st	Ref		Ref		Ref	
Tertile 2nd	1.85 (0.84, 2.86)	<0.001	2.20 (1.28, 3.11)	<0.001	0.78 (0.08, 1.48)	0.029
Tertile 3rd	3.15 (2.14, 4.17)	<0.001	5.47 (4.38, 6.56)	<0.001	1.68 (0.84, 2.52)	<0.001
Trend		<0.001		<0.001		<0.001
Transferrin						
Tertile 1st	Ref		Ref		Ref	
Tertile 2nd	-1.04 (-2.04, -0.02)	0.045	1.47 (0.56, 2.37)	0.001	0.16 (-0.53, 0.84)	0.657
Tertile 3rd	-0.60 (-1.59, 0.40)	0.240	3.23 (2.33, 4.13)	<0.001	0.96 (0.27, 1.65)	0.007
Trend		0.250		<0.001		0.006

Model 1 without any adjustments; model 2 adjusted for age, gender, nationality (Han or others), education (6 years, 6.1–9.0 years, 9.1–12 years, or >9 years), smoking status (current or not current), alcohol consumption (yes or no), total energy intake (quartile), protein intake (quartile), fat intake (quartile) and carbohydrate intake (quartile); model 3 adjusted as for model 2 plus BMI (<18.5 kg/m², 18.5–24.9 kg/m², 25.0–29.9 kg/m², or ≥30 kg/m²) and hypertension.

represented a range of demographic and economic variations in China [24].

The study also has some limitations. Firstly, the majority of our study participants (3748 out of 4509) had a normal range of SF concentrations, and further studies are needed to investigate the abnormal levels of SF on

hypertension development. Secondly, even though numbers of confounders were adjusted, we cannot rule out the possibility that unmeasured factors or residual confounders might contribute to the associations our study observed. Thirdly, the cross-sectional data analysis of the associations between markers of iron status and BP

Table 3 Associations of SF, transferrin and Hb levels with DBP in Chinese adults at baseline.

	Model 1		Model 2		Model 3	
	Coef (95% CI)	P	Coef (95% CI)	P	Coef (95% CI)	P
Serum ferritin						
Tertile 1st	Ref		Ref		Ref	
Tertile 2nd	2.95 (2.36, 4.54)	<0.001	1.45 (0.53, 1.76)	<0.001	0.21 (-0.27, 0.69)	0.396
Tertile 3rd	4.56 (3.98, 5.15)	<0.001	2.30 (1.65, 2.96)	<0.001	0.87 (0.35, 1.38)	<0.001
Trend		<0.001		<0.001		<0.001
Soluble transferrin receptor						
Tertile 1st	Ref		Ref		Ref	
Tertile 2nd	0.44 (-0.16, 1.04)	0.155	0.64 (0.06, 1.23)	0.030	0.51 (0.06, 0.96)	0.027
Tertile 3rd	0.84 (0.25, 1.43)	0.005	1.21 (0.63, 1.78)	<0.001	0.75 (0.30, 1.20)	0.001
Trend		0.005		<0.001		0.001
Haemoglobin						
Tertile 1st	Ref		Ref		Ref	
Tertile 2nd	2.70 (2.11, 3.29)	<0.001	2.71 (2.12, 3.30)	<0.001	1.80 (1.34, 2.26)	<0.001
Tertile 3rd	5.30 (4.71, 5.90)	<0.001	5.73 (5.04, 6.43)	<0.001	3.32 (2.76, 3.87)	<0.001
Trend		<0.001		<0.001		<0.001
Transferrin						
Tertile 1st	Ref		Ref		Ref	
Tertile 2nd	0.57 (-0.03, 1.17)	0.063	1.51 (0.92, 2.09)	<0.001	0.66 (0.21, 1.12)	0.004
Tertile 3rd	1.34 (0.75, 1.93)	<0.001	2.83 (2.25, 3.42)	<0.001	1.35 (0.89, 1.80)	<0.001
Trend		<0.001		<0.001		<0.001

Model 1 without any adjustments; model 2 adjusted for age, gender, nationality (Han or others), education (6 years, 6.1–9.0 years, 9.1–12 years, or >9 years), smoking status (current or not current), alcohol consumption (yes or no), total energy intake (quartile), protein intake (quartile), fat intake (quartile) and carbohydrate intake (quartile); model 3 adjusted as for model 2 plus BMI (<18.5 kg/m², 18.5–24.9 kg/m², 25.0–29.9 kg/m², or ≥30 kg/m²) and hypertension.

Table 4 Associations of SF, transferrin and Hb levels with incident hypertension in Chinese adults.

	Model 1		Model 2		Model 3	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Serum ferritin						
Tertile 1st (−45.97)	Ref		Ref		Ref	
Tertile 2nd (45.97–108.97)	1.39 (1.13, 1.71)	0.002	1.03 (0.83, 1.28)	0.822	0.98 (0.79, 1.22)	0.848
Tertile 3rd (108.97–)	1.74 (1.43, 2.12)	<0.001	1.22 (0.98, 1.52)	0.076	1.09 (0.88, 1.36)	0.437
Trend		<0.001		0.051		0.356
Soluble transferrin receptor						
Tertile 1st	Ref		Ref		Ref	
Tertile 2nd	1.11 (0.92, 1.35)	0.285	1.12 (0.92, 1.35)	0.264	1.14 (0.94, 1.38)	0.195
Tertile 3rd	1.05 (0.87, 1.28)	0.595	1.07 (0.88, 1.30)	0.516	1.09 (0.89, 1.32)	0.404
Trend		0.609		0.529		0.416
Haemoglobin						
Tertile 1st	Ref		Ref		Ref	
Tertile 2nd	1.13 (0.92, 1.38)	0.242	1.15 (0.93, 1.41)	0.203	1.08 (0.88, 1.33)	0.449
Tertile 3rd	1.35 (1.12, 1.64)	0.002	1.45 (1.16, 1.81)	0.001	1.27 (1.01, 1.59)	0.038
Trend		0.002		0.001		0.037
Transferrin						
Tertile 1st	Ref		Ref		Ref	
Tertile 2nd	0.91 (0.74, 1.10)	0.315	1.09 (0.90, 1.33)	0.385	1.08 (0.89, 1.32)	0.444
Tertile 3rd	1.04 (0.86, 1.26)	0.184	1.34 (1.11, 1.62)	0.003	1.26 (1.04, 1.53)	0.017
Trend		0.206		0.003		0.017

Model 1 without any adjustments; model 2 adjusted for age, gender, education (<6 years, 6.1–9.0 years, 9.1–12 years, or >12 years), smoking status (never or ever), alcohol consumption (yes or no), total energy intake (quartile), protein intake (quartile), fat intake (quartile) and carbohydrate intake (quartile); model 3 adjusted as for model 2 plus BMI (<18.5 kg/m², 18.5–24.9 kg/m², 25.0–29.9 kg/m², or ≥30 kg/m²).

make it impossible for us to investigate the causal conclusion on relationship between markers of iron status and BP. However, the prospective association between markers of iron status and incident hypertension suggests that haemoglobin and transferrin levels were positively associated with incident hypertension.

In conclusion, the current study did not detect any association of ferritin or sTFR levels with incident hypertension in the Chinese population. However, we found that haemoglobin and transferrin levels were positively associated with blood pressure and incident hypertension. Further research in different ethnic groups is required to confirm the association between the full range of SF, sTFR, transferrin and haemoglobin concentrations with BP and incident hypertension.

Disclosures

The authors declared that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.numecd.2019.04.012>.

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